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Review of a 5-Year Experience with the Radiostrontium Bone Scintiscan

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G. Joseph Poole, m.d., and Joseph P. Kriss, m.d., *Stanford*

■ *Radiostrontium (^{85}Sr) skeletal scintiscanning was done on 640 cases and 520 were included in a review. Forty-eight percent of 359 patients with biopsy-proved malignant disease had secondary skeletal involvement; in 17 percent the involvement was identified by scintiscanning alone. False-negative scintiscans were recorded in 0.9 percent. Unusual ^{85}Sr localization was found in a bone infarct, in proteus bursitis and in a pulmonary aspergillosis infiltrate. Serum alkaline phosphatase levels were found to be of little value in the evaluation for osseous metastasis, and normal acid phosphatase values in patients with prostatic carcinoma did not exclude the possibility of spread to the skeleton. Both the scintiscan and roentgenograms are essential in the evaluation of patients for metastatic bone disease.*

Since the 1961 report by Fleming et al that administered radiostrontium localizes preferentially in areas of diseased bone,[1] skeletal scintiscanning has proved to be a valuable diagnostic procedure. By this method, bone disease has been identified in 25 to 62 percent of patients who concomitantly had normal skeletal roentgenograms of the same area.[2-6] The greatest value of the scintiscan is in locating the sites of metastasis to bone from primary malignant neoplasms in the breast, lung and prostate, and in locating bone involvement in patients with malignant lymphomas. The scintiscan may be abnormal in a variety of non-malignant diseases including osteomyelitis, Paget's disease, eosino-

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Dr. Poole was a trainee in Academic Diagnostic Radiology supported by USPHS Grant GM 1707 of the National Institute of General Medical Sciences, National Institutes of Health.

Submitted August 26, 1971.

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philic granuloma, hyperostosis frontalis interna, brown tumor, osteogenesis imperfecta, fibrous dysplasia, fractures, osteoarthritis and rheumatoid arthritis.[1,4,7-10] Thus, while the scintiscan locates the site of disease, it does not identify the specific pathologic process, because the increased uptake of radionuclide only reflects an enhanced mineral deposition occurring during bone repair.

Previous reports have been concerned with the role of bone scintiscanning in specific disease states or have included only relatively small numbers of patients. It is the purpose of this paper to describe the results of a study of the sensitivity and specificity of skeletal scintiscanning in a large series of patients done in a single institution over a five-year period.

Methods and Materials

During the period from July 1964 to November 1969, 640 skeletal scintiscans with ^{85}Sr were done in the Division of Nuclear Medicine, Stanford Medical Center. Four hundred and four of these patients had radiographs of the same region of the body taken in the Division of Diagnostic Radiology. In all instances the scan and roentgenogram were performed within one month of each other. The official interpretations of the roentgenograms and scans were tabulated and compared. This analysis resulted in the elimination of nine patients because of inadequate follow-up information. Of the remaining 395 patients (520 scintiscans) 359 were referred for study after the presence of malignant disease had been proved by biopsy. Of the total, 197 were male and 162 were female, and most were older than 40 years. Table 1 lists the primary sites involved and the number of each entity studied. Neoplasms of the prostate, breast, lung and lymphatic system accounted for more than 70 percent of the cases.

TABLE 1.—*Primary Site of Biopsy-Proved Neoplasms*

	No. of Cases
Prostate	74
Breast	70
Lung	39
Hodgkin's disease	52
Non-Hodgkin's lymphoma	27
Leukemia	2
Head and neck	19
Gastrointestinal	19
Urinary tract	14
Female genitalia	10
Multiple myeloma	4
Primary unknown	9
Miscellaneous	20
Total	359

The clinical records of all 395 patients were reviewed and the serum alkaline and acid phosphatase values, when available, were tabulated. The phosphatase determination was performed in the hospital laboratories using the method of Bessey, Lowry and Brock.[11]

A commercial* linear scanner, fitted with a 5-inch diameter thallium-activated NaI crystal and equipped with a 31-hole collimator having a 3-inch focal point, was employed. Both the teledeltos dot scan and film photoscan were obtained, using the technique described by DeNardo and Volpe.[4]

The usual adult dose was 100 uCi of ^{85}Sr given intravenously as the chloride. Children were given 1.4 uCi per kg of body weight. The scintiscanning was performed 48 to 72 hours after administration of the radiopharmaceutical, and after assuring adequate emptying of the colon by the use of laxatives and enemas.

A routine ^{85}Sr scintiscan included study of the thoracic and lumbosacral spine and pelvis. Roentgenograms of the same region were taken at a 72-inch tube-film distance. Lead markers were used so that the roentgenogram and the scintiscan could be superimposed for accurate anatomical localization of the radionuclide. These roentgenograms were not used for diagnostic purposes.

Results

One-hundred and eighty-one of the original 368 patients with known primary malignant lesions had scintigraphic or radiologic evidence, either or both, of tumor involvement of the skeleton. Nine of these, with scintiscan abnormalities alone, were excluded from the study: three who died soon after the examination was performed but were not examined post mortem, two who were lost to follow-up, and four others in whom

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*Picker Magnascanner

TABLE 2.—*Scintiscan and Roentgenographic Results, by Disease Categories*

Malignant Disease (359 Patients)	*+ scan + x-ray*	*+ scan − x-ray*	*− scan + x-ray*	*− scan − x-ray*	*falsely + x-ray*	*falsely + scan*
Primary site						
Prostate	22	1	0	48	2	1
Breast	38	4	3	25	0	0
Lung	18	4	0	17	0	0
Lymphoma	25	9	1	45	0	1
Head and neck	8	3	1	7	0	0
Miscellaneous	24	8	3	39	1	1
Subtotal	135	29	8	181	3	3
Percent of cases positive	79	17	4	...	0.9	0.9
Benign disease (36 Patients)	16	1	3	16	0	0
Total	151	30	11	197	3	3
Percent of cases positive	79	16	5	...	0.8	0.8

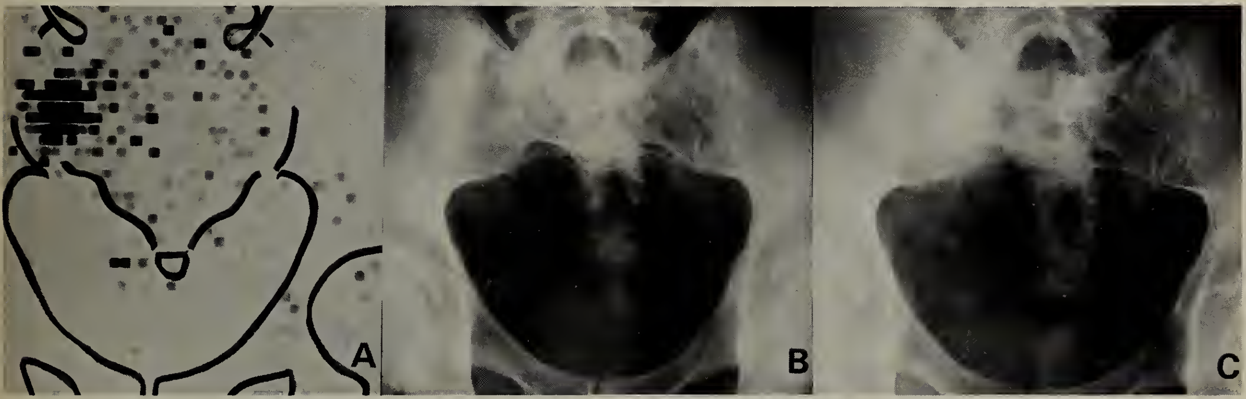

Figure 1.—An example of metastatic bone disease first identified by the scintiscan. The second scintiscan performed in this institution (A) in August of 1964, was on a 68-year-old man with prostatic carcinoma. There is a region of increased isotopic uptake centering over the right sacral ala. The same region on the corresponding roentgenogram (B) was read as negative at that time, although beginning sclerotic involvement can be appreciated. Six months after the original study, a repeat roentgenogram (C) demonstrated the radiodense neoplastic metastatic focus.

evidence of bone disease was not confirmed but who were followed for less than four months. The remaining 172 patients all had evidence of metastatic malignant involvement of the skeleton confirmed by roentgenographic change, biopsy, autopsy or relief of osseous pain by radiation therapy (Table 2). In 29 of these cases the skeletal involvement was first identified by scintiscanning alone (Figure 1).

Thirty-six patients did not have neoplastic disease. In this group, the scintiscan and corresponding roentgenogram was reported as abnormal in 16 patients, including five patients with osteomyelitis, three with acute fracture, two with Paget's disease, and one each with histiocytosis X, osteochondroma, hypertrophic osteoarthritis (Figure 2) and an idiopathic lytic lesion of the skull. Special mention should be made of three other cases because of their unusual nature: (a) radiostrontium localization in an infarction of the left humerus (Figure 3), (b) a case of surgically proven infrapatellar bursitis due to proteus mirabilis which was positive by scintiscanning but negative on roentgenography, and (c) radiostrontium localization within the lesions of pulmonary aspergillosis. In the latter case the involved lung was excised post mortem and was rescanned and radiostrontium concentration

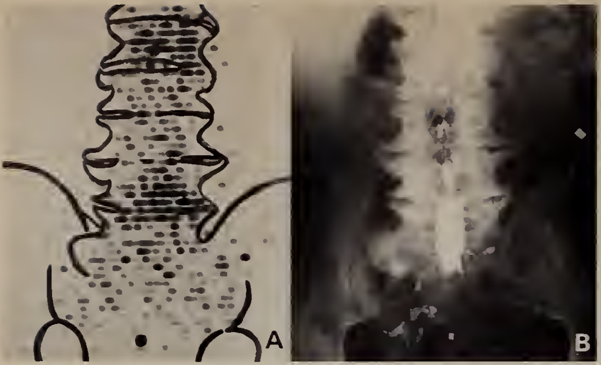

Figure 2.—An 82-year-old man with moderately severe intermittent low back pain was scintiscanned in July of 1966 as part of a work-up for suspected prostatic carcinoma. Although no carcinoma was found then, or during a subsequent 36-month follow-up period, the scintiscan (A) demonstrated several regions of increased ^{85}Sr uptake. The roentgenogram revealed severe involvement with hypertrophic osteoarthritis as shown in (B). There is residual contrast material from a previous myelogram.

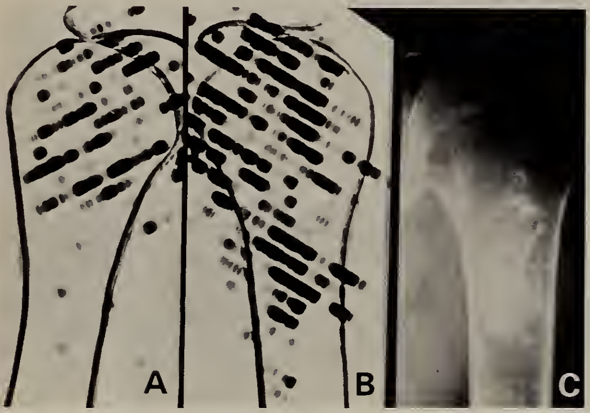

Figure 3.—In contrast to the normal scintiscan of the proximal right humerus (A) the study of the contralateral side (B) clearly depicted a region of increased radionuclide activity in the metaphyseal region in this 61-year-old man who had experienced "stiffness of the arms." The corresponding roentgenogram (C) revealed an irregular, poorly defined density in the same area which, on biopsy, was found to be an infarct.

within the pulmonary lesions was verified. These findings were the subject of a separate report.[12]

. Eleven patients had definite roentgenographic skeletal abnormalities in conjunction with scintiscans initially interpreted as normal. On restudy of the scans, interpretations of bone abnormality were rendered in six cases and one was re-evaluated as "borderline." In one other the scintiscan was of unacceptable technical quality. The other three false-negative scintiscans did not reveal abnormalities upon review.

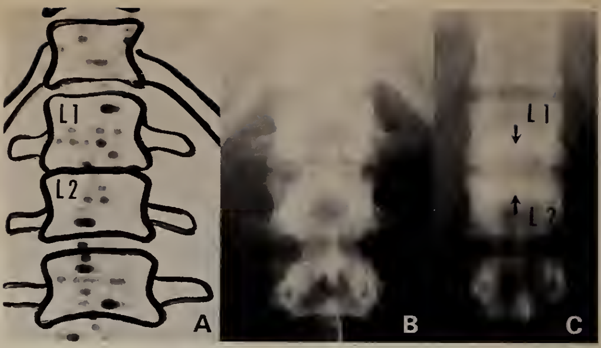

Figure 4.—Osteomyelitis. One of the 3 false-negative scintiscans in our series. A 16-year-old boy presented with fever and severe thoracolumbar spine pain. The scintiscan (A) was entirely normal. However, the roentgenograms (B) and planigrams (C) obtained at the same time revealed narrowing of the lumbar 1 to 2 interspace and early destruction of the adjacent articular plates (arrows).

One of these was performed on a youth with acute lumbar osteomyelitis (Figure 4).

We observed abnormally low strontium concentrations in regions previously exposed to radiation therapy (Figure 5).

Serum alkaline phosphatase determinations obtained within one month of the scintiscan were available on 234 of the 359 patients with known primary malignant disease (Table 3). Of this group, 39 patients were excluded from the analysis because of coexisting liver disease as demonstrated by an abnormal liver scintiscan or biopsy, or elevated serum bromsulphalein, bilirubin, serum glutamic oxaloacetic transaminase or serum glutamic pyruvic transaminase levels. In the remaining 195 patients, 30 had elevated serum alkaline phosphatase and abnormal scintiscan and roentgenograms, while 29 others had a normal serum alkaline phosphatase with positive scintiscan and roentgenogram. Thirteen of 120 patients with normal scintiscans and roentgenograms had elevated serum alkaline phosphatase levels. Ten of these 13 patients were followed for up to 14 months, and one, a man with bronchogenic carcinoma without other evidence of bone disease had a roentgenogram two months after the first scan which demonstrated a destructive lesion of the fifth rib. This area was not included in the first study. The highest correlation between abnormalities in serum alkaline phosphatase levels, scintiscan and roentgenogram occurred in patients with lung carcinoma; the lowest correlation was in patients with breast carcinoma.

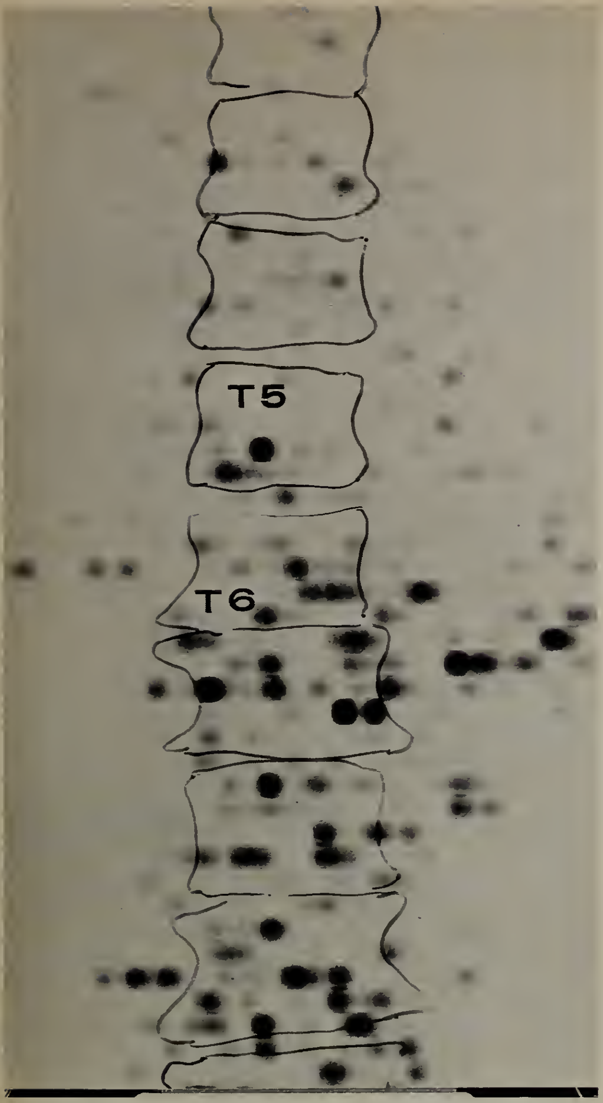

Figure 5.—Reduced ^{85}Sr uptake in the upper thoracic spine as a result of previous radiation therapy. To treat hilar metastatic lesions from an anaplastic squamous cell carcinoma of the lung, 4,100 rads were delivered to the upper mediastinum. The caudal limit of the port was the interspace between the fifth and sixth thoracic vertebra.

Serum acid phosphatase determinations had also been performed in 55 of the 74 patients with prostatic carcinoma. An elevated value was recorded within one month of the scintiscan procedure in ten of the thirteen patients with elevated alkaline phosphatase, and in two of seven patients with normal alkaline phosphatase but with abnormalities on both scintiscan and roentgenogram. Normal serum acid phosphatase was recorded in 25 of the 34 patients who had no evidence of bone disease on either scintiscan or roentgenogram. Elevated values were observed in seven patients with normal alkaline phosphatase, scintiscan and roentgenogram. In six of these seven the alkaline phosphatase determinations were done within 15 days of a prostatic examination or prostatic needle biopsy. In the remaining patient a sclerotic lesion of the eighth thoracic vertebra developed 19 months later.

One hundred and twenty-five of the total of 520 scintiscans were repeat studies, 41 were done as a follow-up procedure, 39 to confirm the initial study, and 45 because of radioisotopic activity in the bowel, or for technical reasons.

Discussion

In our series of 359 patients with documented malignant lesions, 172 had osseous metastasis. The 29 cases that were identified by scintiscanning alone made up 17 percent of that total, a figure which is in agreement with the findings of other investigators.[3,13] In only 4 percent of those with bone metastasis was the osseous lesion identified by roentgenography alone. The greater diagnostic acuity of the scintiscan is due to its ability to detect enhanced bone activity which occurs in response to disease. When new bone is formed, radiostrontium is incorporated in place of calcium and can be identified by scintigraphy. The roentgenogram, however, shows only the net structural change which has occurred, both destructive and reparative.[14]

Prostatic carcinoma was the most frequent single disease entity encountered in this study. Of 74 patients with that disorder, 23 had secondary skeletal involvement—discovered in one case by scintiscan alone, and in none by roentgenogram alone. These results are at variance with those of Morgan and Mills,[16] who found osseous metastasis by scintiscanning alone in 28 of 45 patients (62 percent). However, bone marrow biopsy was done in only four of their patients; an additional 11 had positive scintiscans again recorded six months or more after the first positive scintiscan. In agreement with Morgan and Mills, we found that the serum acid phosphatase was elevated in only about half of patients with abnormal bone scintiscans. Thus, normal serum acid phosphatase would not appear to be a reliable indicator of the absence of bone involvement.

It is perhaps not widely appreciated that ^{85}Sr scintiscanning is effective in identifying osseous

TABLE 3.—*Serum Alkaline Phosphatase Values Compared with Scintigram and Roentgenographic Results in Patients with Malignant Neoplasms*

Site of Primary Malignancy	*No. of Patients*	*Liver Disease*	*No Liver Disease*	*Serum Alkaline Phosphatase*	*+ scan + x-ray*	*+ scan − x-ray*	*− scan + x-ray*	*− scan − x-ray*
Prostate	55	0	55	Elev.	13	0	0	3
				Norm.	7	1	0	31
Breast	44	16	28	Elev.	1	0	0	0
				Norm.	8	2	0	17
Lung	21	3	18	Elev.	7	0	0	2
				Norm.	0	1	0	8
Lymphoma	57	12	45	Elev.	6	2	0	6
				Norm.	5	2	0	24
Head and Neck	16	0	16	Elev.	2	1	0	2
				Norm.	3	0	0	8
Miscellaneous	41	8	33	Elev.	1	3	0	0
				Norm.	6	2	2	19
				Totals Elevated	30	6	0	13
Total	234	39	195	Totals Normal	29	8	2	107

involvement by the lymphomas. There have been several reports of the diagnostic superiority of the scintiscan over the roentgenogram in this form of malignant disease, particularly Hodgkin's disease.[5,15] In the present series, nine of 35 patients (26 percent) with evidence of bone involvement by lymphomas were identified by the scintiscan alone. Moreover, when disease is demonstrable on both the scintiscan and roentgenogram, the extent of involvement often appears greater on the scintiscan.[3,5,16] This supports the contention that scans should be obtained in all patients scheduled for skeletal radiotherapy in order to decide accurately the placement of treatment portals.[13,17,18]

A variety of nonmalignant diseases produce a positive scintiscan. Bauer et al,[19] studying severe osteoarthritis of the knee, found that the regions of most intense radionuclide concentration correspond to the areas of sclerosis as seen on the roentgenograms. Since most of the patients in the present series were older than 40 years, many had roentgenographic evidence of osteoarthritis of the spine. Where involvement was only mild to moderate, scintiscans were normal, but eight of eighteen patients with roentgenographically severe hypertrophic osteoarthritis had increased strontium concentration in the area of roentgenographic involvement (Figure 2). Because of the activity of the process, these patients were experiencing considerable pain.

In our series of 359 patients, false-negative interpretations of bone scintiscans were rendered in three cases—an incidence (0.9 percent) in agreement with previous reports.[3,20,21] Among the reasons given for a false-negative scintiscan are (1) the absence of pathologically stimulated reactive new bone formation, (2) lesions of small size, and (3) lesions so diffuse and uniform as to preclude comparison with normal bone. False-negative scintiscans may be due also to quiescence of a lesion, the reactive process having subsided—a phenomenon that may occur as a result of radiation therapy. In the present series, such cases of lessened strontium localization over treated areas occurred with skeletal doses greater than 2000 rads (Figure 5).

We agree with Posen et al that there is no consistent elevation of serum alkaline phosphatase in patients with skeletal metastatic neoplastic involvement.[22]

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Human Intestinal Nematodiasis in The United States

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■ *Human intestinal nematodes, all of which can be acquired in the continental United States, can cause a variety of ills including iron deficiency anemia, surgical emergencies, eosinophilic pneumonia, malabsorption, dysentery, myositis, and death. The severity of illness is related to the number of parasites acquired exogenously or the ability of the parasite to multiply within the host. Diagnosis of clinically significant infection can usually be made by stool examination, and appropriate treatment requires an understanding of the life-span and pathogenic potential of the parasite.*

INTESTINAL ROUNDWORMS, while most common in underdeveloped tropical countries, can be acquired here in the United States.

The largest and most common roundworm to involve the intestinal tract of man is Ascaris lumbricoides. Accidental ingestion of fertilized eggs results in release of larvae which penetrate the intestinal blood vessels, are carried to the lungs, break out of alveolar capillaries, migrate up the pulmonary tree, and are swallowed. They mature in the small intestine. Adult ascarids lie free in the lumen of the small intestine, maintaining their position by propulsive muscular activity. The life cycle of Ascaris and other helminths is shown in Table 1.

While the stage of larval migration is usually not clinically recognized, occasionally it may be associated with fever, an irritating cough, wheezing, and striking roentgenographic changes of perihilar nodular or lobar densities. This illness resolves spontaneously in seven to ten days. A high eosinophilia, the presence of a papular or urticarial rash in 15 percent of cases, the usual presentation in adults rather than children, and the greater frequency in populations where climate makes ascariasis a seasonal infection, all support the hypothesis that the pulmonary reaction is primarily allergic in nature.[2]

The pathologic importance of adult ascarids derives from the absorption of nutrients from the diet of the host (sometimes causing protein malnutrition in children with borderline diets) and from the peculiar propensity of the adult worm to migrate through small orifices, thereby causing bizarre and sometimes fatal complications secondary to mechanical obstruction of any hollow viscus. Invasion of bilary or pancreatic ducts may produce obstructive jaundice, intrahepatic abscess, pancreatitis or pancreatic abcess. A single worm, migrating up the esophagus, may suddenly obstruct the upper respiratory tract and cause death. A tangled bolus of worms may cause partial or complete intestinal obstruction (most common in the jejunum), or

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TABLE 1.—*Life-Cycle for Intestinal Roundworms of Man*

Worm	*Usual Extrahuman Cycle in USA*[1]	*Route of Entry*	*Pulmonary Migration*	*Usual Prepatient Period*[2]	*Auto-infection*	*Survival of Adult Worm in Man*	*Duration of Infection*
A. lumbricoides	2 weeks	oral	yes	2-3 months	no	1 year	same
hookworm	2-3 days	skin	yes	5 weeks	no	at least 6 years	same
S. stercoralis	0 to months[3]	skin	yes	2-4 weeks	yes	?	up to 36 years
T. trichiura	3 weeks	oral	no	2-3 months	no	months to 3 years	same
pinworm	6 hours	oral	no	2-4 weeks	yes	2 months	years

1. Period from passage in stool to infectivity for man. These time intervals may vary greatly with climate; thus T. trichiuris infective larvae develop within eggs in 6 months at 15°C and in 11 days at 35°C, while the development of infective larvae in the eggs of A. lumbricoides may take from 5 to over 50 days. The duration of infectivity may be considerably longer in a proper environment; thus A. lumbricoides eggs can remain viable and infective for 6 months to six years.
2. Interval from infection to recovery of diagnostic stage (eggs or larvae) in stool of host.
3. Strongyloides infective larvae may develop directly in man, directly in stool (within 24 hours) or may develop into adults which either produce infective larvae or more free-living adult worms.

intussusception (most common at the ileocecal valve), or volvulus. Peritonitis may follow migration of worms through suture lines of surgical operation on the bowel, or (rarely) migration through unmanipulated bowel or following maturation of an ectopic ascarid in the peritoneal cavity. Sauer et al published an excellent review of bizarre obstructive patterns caused by Ascaris.[2] The most common of all intestinal helminths, A. lumbricoides, usually does nothing, but may, on occasion, do almost anything.

Diagnosis at the stage of larval migration is unusual, but a patchy pneumonia associated with a progressive increase in leukocyte count and a concomitant rise in the number of eosinophiles (up to 70 percent) or the demonstration of eosinophiles in the sputum, is suggestive. The diagnosis can be confirmed occasionally when third stage larvae are found in the sputum or gastric aspirate. If ascaris ova, absent in the stool during the acute illness, appear within six months, a retrospective presumptive diagnosis of Ascaris pneumonia can be made. Serologic tests do not distinguish this illness from other larval migrations; indeed, the highest hemagglutination titers are usually to toxocara rather than Ascaris.[1] Diagnosis of the intestinal phase can be made in 95 percent of cases by microscopic stool examination. In 5 percent only adult male worms are present and no eggs are found in the stools. These cases are identified by history (passing a large round worm) or by accident, such as demonstration of Ascarids on roentgenographic examination of the abdomen.

The most effective treatment of Ascaris is with pyrantel pamoate as outlined in Table 2. (Thiabendazole and piperazine citrate are alternate therapies with lower cure rates.) Because of the rare but ever present possibility of a fatal complication even with a single worm, all infections should be treated. Patients with partial intestinal obstruction due to Ascaris can sometimes be managed by nasogastric suction followed by administering piperazine citrate syrup through the drainage tube and repeating the treatment at 12-hour intervals for six doses.[3] Complete obstruction of any hollow viscus is a surgical emergency, and often the cause cannot be determined before laparotomy. After surgical removal of a worm or worms in such cases, pyrantel therapy for any residual infection is indicated.

Hookworm

Human hookworm infection with Ancyclostoma duodenale or Necator americanus is most common in areas where a warm (70-85°F) rainy (over 40 inches of rainfall per year) climate permits maturation of the infective larval stage in the soil and where children go without shoes. Hookworm infection is, therefore, rarely endemic in California, but is common in the Southeastern United States. Skin penetration may be associated with localized pruritis with or without lesions of creeping eruption (ground itch); or it may go unnoticed. The larvae migrate from cutaneous capillaries to the lungs and then follow a cycle similar to that for Ascaris (Table 1). The adult hookworm is attached to the small bowel mucosa by means of cutting plates or teeth, and derives its nutrition by sucking blood from the host.

Although pulmonary migration is occasionally

TABLE 2.—*Chemotherapy of Intestinal Roundworms*

Worm	*Drug*	*Dose (maximum)*	*Duration*	*Cure rate (Percent)*	*Comment*
A. lumbricoides	pyrantel pamoate Antiminth®	10 mg/kg (1 gram)	1 day	>95	Ascariasis is treated first when several parasites are present, because of the theoretical risk of inciting migration of these worms.
Hookworm	tetrachloroethylene	0.12 cc/kg (5 cc)	1 day	>50	Complete worm eradication is not essential; over 90% have reduction in worm burden, all that is necessary to prevent further anemia.
S. stercoralis	thiabendazole Mintezol®	25 mg/kg bid	2 days	>90	Because of autoinfection, worm eradication is always attempted.
T. trichiura	thiabendazole Mintezol®	25 mg/kg bid	2 days	20	Only symptomatic patients are treated.
Pinworm	pyrvinium pamoate Povan®	5 mg/kg (250 mg)	2 days 1 week apart	>90	Only symptomatic patients or families of symptomatic patients are treated.

Note: When more than one worm is present, an alternate drug can be selected for broad spectrum activity. Thiabendazole also has some efficacy against Ascaris, hookworm and pinworm; pyrantel is also effective against pinworm, and pyrvinium pamoate against Strongyloides. Bephenium hydroxynapthoate (Alcopar®) is effective against hookworm and Ascaris. The dose or duration of therapy may differ, however, with mixed infections, and the physician should check the manufacturer's recommendations.

associated with symptoms and some patients complain of abdominal pain simulating that of duodenitis, the majority of infections in the United States are silent. The major pathologic change of hookworm disease is iron deficiency anemia. The importance of any given hookworm infection in the production of iron deficiency anemia can be calculated from the dietary iron plus the number of eggs in the stool. There is an average daily blood loss of 2.1 ml per 1000 Necator americanus eggs per gram of stool, and 4.5 ml lost per 1000 eggs of A. duodenale per gram of stool.[4] Even heavy infections may not cause anemia if the dietary iron is high, but mild infections may bring it about if the diet is borderline. Most adults in the United States have sufficient iron in their diet to tolerate a modest worm burden; they can have hookworm infection without having hookworm disease. Children, particularly those with poor diet, may show severe iron deficiency anemia if heavily infected.

The diagnosis of any clinically significant hookworm infection is easily made by microscopic examination of stool; if concentration techniques are required for demonstration of ova, then it is unlikely there are enough worms present to cause serious pathologic changes. Treatment in the United States should be reserved for food handlers and persons with symptoms or signs of infection; treatment of the asymptomatic carrier for a few worms is not warranted. Most infections will be eradicated by use of tetrachloroethylene (Table 2). In countries where A. duodenale is the primary hookworm, bephenium has been preferred therapy and it has the added advantage that it is also effective against Ascaris.[3] Worm eradication is followed by a very slow correction of iron deficiency anemia; such patients should therefore also receive iron therapy. Indeed, even without worm eradication, iron therapy very promptly corrects hookworm anemia[4] and severe anemia should be corrected before a vermifuge is used.

Strongyloidiasis

Strongyloides stercoralis (threadworm), like hookworm, infects man by skin penetration and pulmonary migration. But no soil phase is required, as it is with hookworm, for maturation of infective larvae. Strongyloides larvae may mature to the infective filariform stage while passing through the large intestine and reinvade the host through the colonic mucosa or perianal skin. Autoinfection is responsible for the extremely heavy intestinal parasitism seen in some patients and the persistence of infection long after the host has left an endemic area.

Although creeping eruption is far oftener caused by threadworm than by hookworm, skin penetration frequently goes unnoticed. All larvae, whether of exogenous or endogenous source, migrate through the lungs. Symptoms of larval migration are similar to those described for Ascaris pneumonia; patients typically have pneumonitis, fever, urticaria and pronounced eosinophilia. X-ray films of the chest may show almost any changes, including diffuse miliary densities very suggestive of tuberculosis. An allergic reaction, as described for ascariasis, is suggested by the common finding of urticaria. Autoinfection also can produce a massive simultaneous pulmonary migration unlikely to occur with an exogenously acquired parasite; in these cases a large part of the pulmonary complex may actually be due to migrating larvae. In fatal cases pulmonary hemorrhages are common.

The adult organisms, which lie embedded in the mucosa of the duodenum and jejunum, usually cause no symptoms. Some patients experience epigastric pain that clinically and radiographically mimics duodenal ulcer. Massive involvement of the small intestine is sometimes associated with frank malabsorption,[5] but some patients tolerate extremely heavy infections without absorption deficiency.[6] Massive autoinfection can occur, often but not always precipitated by corticoid therapy.[7] In such cases patients have vomiting, diarrhea, fever, pulmonary abnormalities; frequently there is neither peripheral eosinophilia nor the presence of parasites in the stool to afford clues to diagnosis. Such cases may be fatal. Major findings at autopsy include the observation of adult forms, larvae and ova in the wall of the small intestine, and severe changes suggestive of granulomatous or ulcerative colitis in the large intestine.[8] Parasites are also found in many other tissues.

The diagnosis of strongyloidiasis is usually made by identification of larvae in fresh stool; Strongyloides ova are rarely found in the stool in the absence of diarrhea, and hookworm larvae, which have subtle morphologic differences from those of S. stercoralis, are not found in fresh stool. The yield from stool examination can be enhanced by suspending approximately 100 grams of fresh stool in fine surgical gauze over a glass, adding lukewarm water to the level of suspended stool so that the bottom of gauze and water are in contact, and waiting one hour for larvae to migrate through the gauze and drop to the bottom of the glass. The sediment is examined for larvae. Eight stool examinations will lead to diagnosis in more than 80 percent of cases, but in some patients, where internal autoinfection is complete, no parasites will be found on stool examination. One duodenal or, better, jejunal drainage specimen is equivalent to eight stool specimens and will establish the diagnosis in almost all cases. The treatment of choice today is with thiabendazole in doses outlined in Table 2. Although the majority of infections are asymptomatic, the possibility of autoinfection and and even death makes treatment advisable.

Trichuriasis

Whipworm infection is acquired by inadvertent ingestion of infective eggs and therefore coexists with A. lumbricoides. The worms mature in the large intestine without a migrational phase, and the adult female can lay several thousand eggs daily. As with hookworm, the soil cycle is required for maturation of eggs to the infective form.

The majority of infections in the United States are light and asymptomatic; symptoms rarely occur in patients with less than 10,000 eggs per gram of stool. When heavy infection produces illness, diarrhea is the most common complaint. Rectal prolapse may follow, with myriads of small white worms seen covering the rectal mucosa. Dysenteric trichuriasis is often associated with amebiasis. Because the Trichuris sucks blood as well as causing dysentery, heavy infections may also cause iron deficiency anemia. One Trichuris ingests approximately 0.005 ml of blood per day, which is 6 to 10 times less than that obtained by N. americanus and 50 times less than by A. duodenale. However, with over 5 million eggs per day—that is, over 800 whipworms—the blood loss may reach 4 ml a day (1.5 mg of iron) which can ultimately cause iron deficiency anemia.[9]

Because only heavy infections produce symptoms, diagnosis can readily be made on microscopic stool examination. Unfortunately treatment is less simple. Thiabendazole (Table 2) generally considered to be the drug of choice, is curative in only 20 percent of cases. Hexylresorcinol retention enemas using about 500 ml of 0.2 percent aqueous suspension for one half hour, repeated at four-day intervals three to four times, may be worthwhile in highly symptomatic patients who do not respond to thiabendazole.[3] The perianal area must be widely protected by petroleum jelly. A new agent, dichlorvos, seems to be promising for treatment, but is currently available only for investigational use in the United

States. A five-day course of treatment with dithiazinine, which is no longer available for clinical use in the United States, was curative in over 95 percent of cases.[3]

Enterobiasis

Pinworm infection, the most prevalent helminth infection in the United States, follows ingestion of the embryonated eggs of Enterobius vermicularis. They mature into adults without extra-intestinal migration and live unattached in the lumen of the lower small intestine and upper large bowel. The gravid adult female migrates, usually at night, to the perianal area and disintegrates, releasing 4,000 to 17,000 sticky eggs. This phenomenon is associated with pruritis ani; resultant scratching transfers eggs to the fingers, thus to the mouth, and external autoinfection ensues. Eggs may also hatch in the anal area and larvae may reinfect through the colon—retroinfection. Eggs also persist on clothing and sheets and probably are spread as an aerosol, leading to infection of the entire family.

Although at least 25 percent of children in general (and half of their family members—including adults) and over 90 percent of children in institutions are infected with pinworms,[10] the vast majority of infections are asymptomatic and unsuspected. Symptomatic patients are usually children, probably owing to their propensity to put fingers in and around body orifices sequentially, leading to heavy autoinfection. The ubiquity of the parasite has led to its incrimination in a variety of conditions which include nagging wives and accident proneness.[11] More reasonable but equally undocumented are rectal bleeding and acute appendicitis; in both, the association of pinworms seems to reflect their geographic prevalence rather than an etiologic role. The only clear-cut pathologic change is one that is essential to the perpetuation of parasitism, pruritis ani; it is possible that mild insomnia and irritability do result from this annoying symptom. More rarely, abdominal pain, urethritis or vaginitis appear to be due to this parasite.

The diagnosis is made by placing cellulose tape, sticky side down, on the perianal area in the morning before bathing, sticking the same tape to a glass slide and examining it microscopically at leisure. Diagnosis is made in virtually all cases if this examination is done on three consecutive mornings. Although eggs are occasionally found in urine and stool, neither method affords a reliable means of diagnosis.

Treatment with pyrvinium pamoate (Table 2) is 80 percent effective in a single dose and a 93 percent cure rate is achieved by repetitive therapy of three weekly doses. Because pinworm is classically a family infection, parasite eradication requires simultaneous treatment of the entire family. A one-day course of treatment for the family is generally recommended only when there is a symptomatic member. Because it is known that eggs are disseminated in the home environment and can remain viable for up to three weeks, vigorous cleaning is often recommended to prevent reinfection; but that measure is ill-advised, for it is ineffective and serves only to place unwarranted importance on this infection.

Trichinosis

Whereas man serves as the only source of his other intestinal nematodes, Trichinella spiralis is a zooinosis and man is an accidental host. Two hosts are necessary for perpetuation of the life-cycle and each host is infected with the larval and the adult form. Man, swine and other carnivores become infected when they ingest meat containing viable larvae. Larvae excyst in the intestine, mature to adults and mate. The fertilized female then burrows into the intestinal mucosa, releasing larvae into blood and lymph. Release of larvae occurs about five days after fertilization and continues for two to six weeks; each female can release more than 1,000 larvae. Larvae that are carried to striated muscle survive, grow rapidly and encyst in about three weeks. They may remain viable for years even when calcification of the cyst wall ensues.

In the absence of cannibalism, man is a dead-end host. He usually becomes infected from eating inadequately cooked pork, often in the form of locally-made sausage, although bear and other wild animal meats have led to occasional outbreaks. Pigs become infected from ingestion of untreated garbage, dead rodents, or the carcasses of other dead animals. The prohibition of feeding uncooked garbage to swine since the mid-1950's and the increasing use of frozen meats* have been important in reducing the incidence of reported trichinosis in the United States from 487 cases in 1948 to 84 cases in 1968.[12] U.S. inspection of pork does not include microscopic examination for the cysts of T. spiralis, and only adequate cooking of pork products insures its safety. Trichinosis is an incidental finding in about 5 percent of autopsies in North America today.[13] Parenthetically, many recent outbreaks of trichinosis, including one in California, have been related to the ingestion of the flesh of wild animals, especially bear meat.

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*While data is lacking on freezing schedules for large cuts and whole carcasses, in cuts of pork for home use T. spiralis is killed by freezing at 5°F for 20 days or at −20°F for six days.

The majority of infections are mild and asymptomatic. Heavy infection may be associated with gastroenteritis at the stage of burrowing of the fertilized adult, but usually this phase goes unnoticed. Initial symptoms typically occur the second week after ingestion of the infected meat, and are characterized by periorbital edema, headache, myalgia, dyspnea, neurologic abnormalities, mucocutaneous hemorrhages, rash and fever. It may be that not all of these manifestations are present in any given patient. Eosinophilia is virtually universal in recognized cases, but may disappear before death. Symptoms continue for up to six weeks, and complete recovery is often delayed for several months. Although larvae do not encyst in the myocardium, pronounced myocarditis is usual in fatal cases.

Fever, myalgia, periorbital edema and splinter hemorrhages under the nails in a patient with eosinophilia strongly suggest the diagnosis of trichinosis. In contrast to most other acute febrile diseases, the erythrocyte sedimentation rate is frequently normal.[14] Creatinuria and elevation of muscle specific enzymes such as creatininephosphokinase (CPK)and lactatedehydrogenase (LDH), such as are seen with myopathy of other kinds, are frequently noted. Specific diagnosis can sometimes be made by serologic testing (complement fixation, fluorescent antibody, and others). A complement fixation test with high specificity is usually positive within one week of illness, but the results may be negative in proved cases.[14] Muscle biopsy of any tender muscle provides the best means of definitive diagnosis. Serial sections may be necessary to demonstrate that the myositis is associated with larval infiltration. A crush preparation of unfixed muscle gives a better yield; motile larvae can usually be demonstrated, often in the tisue fluid at the edge of the specimen. Skin testing is best suited for detection of more remote infection, and may be negative in 15 percent of acute cases.[14] Examination of feces for adult worms is usually unsuccessful.

Because of the extremely variable course of illness, the efficacy of any therapy has been difficult to assess. In most clinically recognized cases the patients do very well with aspirin and supportive therapy, while a few require corticosteroids in full dosage. Thiabendazole, 25 mg per kg of body weight twice a day for 10 to 21 days, has been considered effective in some cases; fever and pain usually resolve within three days, and degenerated larvae can be demonstrated on muscle biopsy following therapy, but other laboratory abnormalities such as eosinophilia and muscle enzyme elevations are unaltered.[14] Drug intolerance, usually nausea and vomiting, may preclude completion of therapy.

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Lactic Acidosis with Phenformin Therapy

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■ *Nine cases of severe acidosis occurring in patients with maturity onset diabetes who were receiving phenformin therapy were reviewed. All had evidence of renal disease. Lactic acidosis was diagnosed by elevated blood lactate levels in seven patients, and by the clinical manifestations and laboratory information in the other two. Contributing factors are discussed, as well as means of treatment and prevention. Although the specific etiology of renal disease is not emphasized in this paper, unrecognized progressive deterioration of renal function is implicated in the etiology of lactic acidosis.*

INCREASED BLOOD LACTIC ACID levels associated with phenformin (N′-betaphenethylbiguanide) therapy have been described since the introduction of the drug. A profound state of metabolic acidosis associated with a striking elevation of lactic acid has long been recognized as a potential hazard in its use.[1,2,3,4] The general subject of lactic acid acidosis was excellently reviewed recently,[5] and there appear to be multiple causes contributing to the condition. Phenformin therapy in diabetic patients and evidence of underlying renal disease, two of these etiologic factors, were present in nine cases of lactic acidosis recently recognized at the San Joaquin General Hospital. Five of these cases are presented because of the widespread use of phenformin in maturity onset diabetes and to support a recommendation that phenformin be included in the general reevaluation of the role of oral hypoglycemic agents in diabetes.

Case 1. A 51-year-old white man was admitted with a history of two days of nausea, vomiting, abdominal pain and progressive shortness of breath. Three years earlier, an anterior and posterior resection had been performed for adenocarcinoma of the rectum. He had been in hospital a month previously with obstructive nephropathy thought to be due to benign prostatic hypertrophy. Three days before admission, nitrofurantoin had been started for a urinary tract infection. Medications were digoxin 0.25 mg a day and phenformin 50 mg capsules (DBI-TD®) twice daily, which he had taken for five months since discovery of adult onset diabetes mellitus.

The patient was lean, weak, oriented and dyspneic. Blood pressure was 165/75 mm of mercury and respiratory rate 32 per minute. Surgical scarring compatible with the history was present on the abdomen, mild AV nicking was noted in the optic fundi, and the patient was pale. There were no other significant abnormalities.

Laboratory results included blood sugar of 150 mg per 100 ml, hematocrit of 31 percent and creatinine of 6.0 mg per 100 ml. The venous pH was 6.93, the pCO_2 23 mm of mercury, potassium 6.7 mEq per liter and plasma bicarbonate 5 mEq with a base deficit of 24 mEq. Sodium was 139 mEq per liter and chloride 98 mEq. A presumptive diagnosis of lactic acidosis was made and four liters of fluid with 360 mEq of sodium bicarbonate* were given in the next

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*The bicarbonate requirement in mEq, to be found in standard textbooks, may be rapidly calculated as follows by use of an arterial blood gas determination: the "base deficit" in milliequivalents per liter is simply multiplied by the "bicarbonate space" in liters. The latter figure is roughly 45 percent of the body weight in kilograms for both adults and children (one liter weighs one kilogram). Thus, sodium bicarbonate required for a 70-kilogram patient with a base deficit of 20 milliequivalents per liter would be derived as follows: NaHCO3 required = 0.5x70 kg × 20 mEq/L = 700 mEq. Any overestimate inherent in this method is overshadowed by the urgency of the clinical situation and the need for continued blood gas monitoring.

24 hours, two-thirds of it in the first six hours. The creatinine was 4.1 mg per 100 ml by this time, with creatinine clearance of 15 ml per minute and the blood urea nitrogen was 96 mg per 100 ml. The lactic acid level before institution of therapy was 173 mg per 100 ml (normal levels of 5 to 20 mg, BioScience Laboratories).

The subsequent hospital course was uneventful. Values for SGOT, SLDH, and SCPK were normal throughout.

Case 2. The patient was a 63-year-old Mexican-American woman with a history of diabetes mellitus for 25 years, easily controlled by 30 units of NPH insulin a day. Urinalysis on several occasions over a two-year period showed 2+ proteinuria, with urine pH averaging 5.5. Because of her obesity and relatively low insulin requirement, an attempt was made to control hyperglycemia with one phenformin capsule three times a day. This was successful, as judged by the clinical appearance and the blood sugar determination, and insulin was discontinued. The blood sugar remained satisfactory, and the patient did well for two months, when she began having mild diarrhea associated with abdominal pain, vomiting and lethargy.

On examination, the patient was observed to be acutely ill, diaphoretic, obese, oriented and eupneic, with respirations 22 per minute and a blood pressure of 80/60 mm of mercury. The rectal temperature was 36.4°C (97.6°F), the pulse 75 and regular.

Laboratory data on admission showed blood sugar of 273 mg per 100 ml and serum acetone reactive at 1:2 dilution. The arterial pH was 6.80, the pCO_2 15 mm of mercury, the plasma bicarbonate undetectable, and the base deficit 32 mEq per liter. The potassium was 6.6 mEq, sodium was 137 mEq, the chloride was 87 mEq per liter. The blood cell count was not remarkable except for hematocrit of 33 percent. Normal values for SGOT, SLDH, SCPK, and amylase were obtained.

A presumptive diagnosis of lactic acidosis was made, but unfortunately a blood specimen for lactate and pyruvate was lost. The bicarbonate required to correct the serum acidosis was rapidly calculated, and 160 milliequivalents of $NaHCO_3$ was given with two liters of 5 percent dextrose in one half normal saline solution as fast as possible.

An x-ray film of the chest showed passive pulmonary congestion, and digitalization was begun. The patient was given 40 units of regular insulin intravenously and subcutaneously. Antibiotic therapy for pyuria was begun.

Twelve hours later, the acidosis was corrected and the patient had received 8 liters of fluid, 80 units of regular insulin, and 850 mEq of sodium bicarbonate. At this time, the pH was 7.56, the plasma bicarbonate 24 mEq per liter, the pCO_2 40 mm of mercury and the potassium 3.2 mEq per liter. Serum acetone was positive undiluted; blood sugar was 185 mg per 100 ml. Eight hours later, the urine became alkaline and large amounts of acetone appeared in it. Serum creatinine of 2.6 per 100 ml with a creatinine clearance of 33 ml per minute was subsequently demonstrated. The hospital course thereafter was uneventful and the patient was discharged with prescription of 40 units of NPH insulin daily.

Case 3. The patient was a 49-year-old black woman with diabetes of three years' standing that was controlled with phenformin 50 mg capsules and diabinese 250 mg, each three times a day. For three days before admission she had progressive shortness of breath. Serum creatinine was 1.6 mg per 100 ml and creatinine clearance was 41 ml per minute.

On physical examination the patient was observed to be disoriented and obese. Blood pressure was 100/60 mm of mercury, deep respirations were 40 per minute and the rectal temperature was 37°C (96.8° F). The pulse was 100 a minute. The neck veins were distended with the patient sitting at 30 degrees, and rales were present at the left posterior lung base. There was a grade II aortic systolic murmur.

Laboratory studies of significance included blood sugar of 48 mg per 100 ml, negative serum acetone, pCO_2 of 15 mm of mercury, arterial pH of 6.98 and potassium of 6.0 mEq per liter. The plasma bicarbonate was 4.5 mEq per liter with a base deficit of 22 mEq per liter. Sodium was 136 mEq and chloride 105 mEq per liter. Normal values for SGOT, SLDH, SCPK, and amylase were obtained. The hematocrit was 35 percent. The lactate-pyruvate determination was 153 mg/3.5 mg per 100 ml (normals 5 to 20/0.3 to 0.9, Bio-Science Laboratories).

Treatment during the first four hours included administration of 2 liters of fluid and 570 milliequivalents of sodium bicarbonate. As the central venous pressure rose, the blood pressure fell. Digitalis, furosemide, and isoproterenol drip were initiated. By this time the blood sugar was 173 mg per 100 ml, the pH 7.22, the pCO_2 22 mm of mercury, the plasma bicarbonate 9 mEq per liter and the base deficit 18 mEq per liter. Urine sugar and acetone determinations were negative. Nine hours after admission, the patient had received 1,220 milliequivalents of sodium bicarbonate with 4.5 liters of fluid, and the central venous pressure had begun to decline. In spite of this apparent improvement, the pH dropped to 7.00. Shortly thereafter, she died. Nephrosclerosis and passive congestion of the liver were found at autopsy. Pneumonitis was not present.

Case 4. An 80-year-old white man was admitted, without subjective complaints, because of cardiac arrhythmia. He was taking digoxin 0.25 mg a day, phenformin 50 mg capsules twice a day, tolbutamide 500 mg four times a day, reserpine 0.25 mg twice a day and Dyazide® once daily.

The pulse was irregular, averaging 80 beats a minute, blood pressure 180/90 mm of mercury, and respirations quiet at 20 per minute. Grade II atherosclerotic changes were present in the optic fundi, a grade III aortic ejection murmur was heard, and a large amount of pitting ankle edema was present. The hematocrit was 37 percent, blood sugar was 110 mg and BUN 26 mg per 100 ml, plasma bicarbonate was 19 mEq per liter and the electrolytes were normal. There were 15 to 20 hyaline casts per field in the urinary sediment.

Phenformin and tolbutamide were continued, digoxin was discontinued, and the arrhythmia was treated with lidocaine and propranolol. The creatinine was found to be 1.4 mg per 100 ml and the creatinine clearance was 71 ml per minute. The patient was cautiously redigitalized with 0.125 mg digoxin daily, beginning the seventh hospital day. Blood sugar at this time was 66 mg per 100 ml. Five hours later, the patient became restless, although the vital signs remained stable, including eupnea at a rate of 24 per minute. The urine sugar and acetone determinations were negative, and the urinary output was satisfactory. Laboratory values included arterial pH of 6.80, pCO_2 less than 4 mm of mercury, plasma bicarbonate of 5 mEq per liter and a base deficit of 22 mEq per liter. Serum potassium was 6.5 mEq per liter. The SGOT and SCPK were normal. A repeat blood sugar determination was 168 mg per 100 ml and creatinine 5.6 mg per 100 ml. The patient died before appropriate therapy was begun. Nephrosclerosis and nodular prostatic hyperplasia were found at autopsy. No serum lactate level was obtained.

Case 5. A 67-year-old senile white woman presented with lethargy and disorientation of five hours' duration and nausea and vomiting for one day. The only other illness known was hypertension, for which she received phenobarbital, 30 mg three times a day, chlorhydrothiazide 500 mg daily, alphamethyldopa 250 mg twice a day, reserpine 0.25 mg twice a day and potassium chloride 1 teaspoon twice a day. Additionally she took chlorpromazine 25 mg at four-hour intervals as needed, and had taken phenformin 50 mg twice a day for six years. She had been in hospital five months before this admission for an exacerbation of abdominal pain of two years' duration. Upper and lower gastrointestinal series, liver enzymes, and amylase were all normal at that time, and no diagnosis was reached.

On examination, the patient was noted to be lethargic, disoriented and obese. Blood pressure was 120/60 mm of mercury, respirations 28 per minute, pulse rate 70 and regular, temperature 35°C (95°F) rectally. She was pale, had moderate ankle edema, and rales at both lung bases. There were no localizing neurologic signs.

Urinalysis showed large acetone content and 2+ protein. The hematocrit was 33 percent, blood sugar 135 mg per 100 ml without acetonemia. An arterial blood pH was 6.84, plasma bicarbonate 3 mEq per liter, pCO_2 26 mm of mercury, with a base deficit of 22 mEq per liter, potassium was 4.3 mEq and sodium 147 mEq per liter. At this point, lactic acidosis was diagnosed. Central venous pressure was 11 cm of water. In the next 90 minutes 400 mEq of sodium bicarbonate was given, bringing the arterial pH to 7.24, with the plasma bicarbonate 8 mEq per liter and the remaining base deficit 19. After administration of 578 mEq of bicarbonate in the next five hours, pH was 7.27, plasma bicarbonate 5 mEq and base deficit 14 mEq per liter.

Although the central venous pressure was stable, the sodium content was 158 mEq per liter by this time, and the potassium 4.6 mEq. The patient had received a total of 25 units of regular insulin, as the blood sugar had climbed to 153 mg per 100 ml, and 320 mEq of potassium

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chloride in 4 liters of one-fourth normal saline solution. In addition, she had been digitalized and had a good urinary output.

Since it was apparent that the patient had reached a critical point between salt overload and lack of complete response to alkali, tromethamine was tried, intravenously. She required no subsequent bicarbonate, and within three hours the pH was 7.37 and plasma bicarbonate 14 mEq per liter. Seventeen hours after admission, the pH was 7.51 and the plasma bicarbonate 35. Twenty-four hours after admission, the pH was 7.40. The serum creatinine was 2.1 mg per 100 ml and blood urea nitrogen 28 mg per ml. During the first three hospital days, these maximum enzyme levels were reached: SLDH 696, SGOT 500, SGPT 40, SCPK 504. Several serum amylase determinations were normal. Serial electrocardiograms revealed old anteroseptal myocardial infarction and nonspecific ST-T wave changes which persisted throughout the hospital stay, which was subsequently uneventful. The creatinine stabilized at 1.8 mg per 100 ml. Serum lactate was 308 mg and pyruvate 3.1 mg per 100 ml.

Four additional cases are summarized in Table 1.

Discussion

Phenformin is thought to inhibit oxidate metabolism at the cellular level and to increase anaerobic metabolism with a resultant increase in lactic acid production.[3,4] Excretion of the drug is decreased with renal dysfunction. Lactic acidosis as a distinctive and potentially lethal syndrome is known to be a risk with high doses of phenformin, or with excessive retention of low doses. Small rises in blood lactic acid levels may be found with phenformin doses only slightly above the recommended maximum of 150 ml per day.[1] Thus, it would appear that since excretion of phenformin is via the kidneys, decreased renal function may cause excessive retention of the drug, which in turn may increase the anoxic proportion of cellular metabolism.

Other causes of tissue anoxia may accelerate the process, especially shock of any cause.[4] Additional frequently found factors are ethanol consumption, infection—especially pyelonephritis—and uncontrolled diabetes mellitus. The syndrome is occasionally seen in leukemia and in type I glycogen storage disease. It has also occurred without known cause.

Recognition of the syndrome of lactic acidosis in diabetic patients requires an awareness of the above factors in a patient with a severe metabolic acidosis out of proportion to the blood glucose and acetone levels. The urine sugar and acetone are usually absent to moderately elevated, although they may be up sharply. The blood lactate level is elevated and the pH is depressed, usually profoundly by the time the disease is recognized.

It can be appreciated from the foregoing that the toxic effect of excessive phenformin levels, presumably anoxic metabolism, can be coupled with that of shock of any cause, particularly in the face of the increased oxygen demands of infection. In such circumstances, as shock begets shock, the shock of lactic acidosis becomes an autoaccelerating phenomenon.

Treatment, because of the truly emergency nature of the illness, must be prompt and aggressive; yet, even so, the prognosis is poor. The basic principles remain:

1. Correct the underlying cause, withdrawing phenformin.

2. Correct any causes of anoxia or shock, such as acidosis, hypovolemia, sepsis, diabetic ketoacidosis, pain, hypoglycemia, severe anemia, or correctable causes of renal failure.

In the cases presented, phenformin was discontinued; the shock was treated with blood volume expansion by intravenous fluids, and a large proportion of the calculated base deficit was given rapidly. We prefer an intravenous administration of 60 to 100 percent of the bicarbonate requirement in one to six hours. Requirements for insulin can be judged principally by blood sugar, and acetone, as is usual with uncomplicated diabetic ketoacidosis.

Dialysis may become a most important therapeutic regimen in patients who cannot tolerate large sodium or fluid loads. It may be hypothesized that bicarbonate buffering would be of greater benefit than acetate or lactate buffering, although this does not presuppose that excess lactate ion is in itself toxic. However, since the pyruvate-lactate equilibrium is in favor of lactate, and the latter must be metabolized to bicarbonate via pyruvate to act as a buffer, lactate is an inefficient buffer in this disease. This should be an early consideration if hemodialysis is unavailable. However, use of this drug is controversial.[8,9]

Table 1.—*Patient Characteristics*

Patient	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Age, Sex	51 M	63 F	49 F	80 M	67 F	54 F	72 F	63 F	70 M
Symptoms,									
Cerebral		lethargic	disoriented		lethargic, disoriented		confused	confused	
Abdominal	pain, nausea, vomiting	pain, diarrhea vomiting		diarrhea	vomiting		nausea	nausea, pain	
Other	dyspnea		dyspnea			dyspnea			
Phenformin 50 mg	bid	tid	tid	bid	bid	bid	qid	bid	bid
Creatinine (mg per 100 ml)	6.0	2.6	1.6	5.6	2.1	3.7	2.5	2.7	1.5
Urinalysis	normal	protein++ WBC 15	normal	normal	acetone-large, protein++	normal	acetone-small, WBC few, protein++	acetone-small	WBC 6-8
Other evidence of renal disease	obstructive nephropathy pyelo-nephritis						pyelo-nephritis	urethral stricture	
Evidence of liver disease						alcoholic			alcoholic
Evidence of vascular disease other than diabetes mellitus	✓		✓	✓	✓	✓	✓	✓, pacemaker	✓
Blood pressure	165/75	80/60	100/60	180/90	120/60		120/70	60/40	138/70
Blood sugar/acetone	150/0	123/1:2	48/0	66/0	135/0	251/small	270/0	78/trace	28/0
Packed red cell volume %	31	33	35	37	33	38	31	32	37
pH*	6.93	6.80	6.98	6.80	6.84	6.85	7.07	7.14	7.03
Bicarbonate mEq/L	5	0	4.5	5.0	3	8	8	9	7.5
Therapy-liters	4	8	4.5		4		4	7	5
Bicarbonate mEq/L	360	850	1220		978		792	704	440
Tromethamine					✓		✓		
Lactate/Pyruvate, mg per 100 ml	173/–	–	153/3.5	–	308/3.1	120/1.7	127/3.8	285/3.5	178/4.5

*Arterial in all but Case 1.

Tromethamine may offer an acceptable alternative to huge loads of sodium bicarbonate, especially with extreme pH depression, or in patients with significant cardiac disease.

The patients presented had as a common denominator phenformin therapy for diabetes in doses of 100 or 150 mg per day, and probable renal disease. Mild anemia was present in all cases. Symptoms of abdominal pain experienced by Cases 1, 2, 5 and 8 could be explained by uncontrolled diabetes mellitus or a side effect of phenformin, although pancreatitis has been described as a common complication of lactic acidosis.[6] The diarrhea seen in Cases 2 and 4 and vomiting and nausea in Cases 1, 2, 5, 7 and 8 may be due to the same cause, although digoxin toxicity may have contributed in Case 4. Cases 2, 3, 5, 6, 7 and 8 were mildly to moderately hypothermic before fluid therapy, and the patients in Cases 3, 4, 5, 7 and 8 experienced altered consciousness.

Shortness of breath was prominent in Cases 1, 2 and 4. Although the patient in Case 1 was under treatment with nitrofurantoin, no pulmonary infiltration was apparent on chest roentgenograms. We have no explanation of why there was no hyperpnea or tachypnea in Cases 2, 4, 5 and 8.

The rather low blood sugar obtained early in the course of Case 3 may have been due to excessive retention of chlorpropamide as well as phenformin, on the basis of chronic renal disease. Only phenformin is likely to have accounted for this in Cases 4, 8 and 9. It is evident that low blood sugar has no general predictive value in reference to the onset of lactic acidosis.

Enzyme elevations may be obtained in shock without implication of other underlying cause. However, as in severe diabetic ketoacidosis, the authors recommend a routine electrocardiogram on the third hospital day of lactic acidosis therapy. Clinical myocardial infarction did not develop in any of the nine cases, although the patient in Case 5 was watched with special care.

The unifying factor in each case was decreased renal function. Certainly, none of the patients presented had "a uremic picture." However, it is well recognized that 50 percent renal nephron destruction may occur before a significant rise in blood urea nitrogen or creatinine appears. More subtle signs were available, such as the 2 plus proteinuria of Case 2 or the creatinine clearance of 71 ml per minute in Case 4. The presence of artherosclerotic disease with increasing age, coupled with the potential of Kimmelstiel-Wilson disease in any patient with diabetes forces the conclusion that decreasing renal function is to be expected in any diabetic. An additional misleading facet is that of marginal renal function, which may drop sharply under stress yet speedily return to previous levels without significant additional loss of nephrons.[7] The problem, then, is anticipating the stresses, some of which have been discussed above, and defining the meaning of the word *marginal*.

Since it is well known that the serum creatinine and blood urea nitrogen do not reflect subtle renal disease, we are currently using 90 ml per min as a minimum creatinine clearance before prescribing phenformin, since in our experience significant retention of the drug may occur below this level.

Gradual deterioration of renal function or any acute intercurrent illness causing depression of renal function can result in the occurrence of lactic acidosis in patients who apparently have tolerated phenformin therapy for some time. This drug should certainly never be given in presence of elevated blood urea nitrogen or creatinine, and creatinine clearance should be determined in all other patients before selecting it as the drug of choice. The physician must choose candidates for phenformin therapy with considerable discretion and then be constantly alert to complications.

TRADE AND GENERIC NAMES OF DRUGS

DBI-TD®	*phenformin*
Orinase®	*tolbutamine*
Dyazide®	*triamterine with hydrochlorothiazide*
Diabinese®	*chlorpropamide*
Hydrodiuril®	*hydrochlorothiazide*
Aldomet®	*alphamethyldopa*
Thorazine®	*chlorpromazine*
Tham-E®	*tromethamine*

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Microwave and Man

The Direct and Indirect Hazards, and the Precautions

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■ *Microwave-radar is a form of electromagnetic energy with potential hazards to human health and safety. Its lethal and non-lethal harmful effects have been demonstrated in experimental animals. Lethal effects upon humans from exposure to microwave have not been proved. Alleged non-lethal effects have been limited primarily to cataractogenesis. Increasing use of microwave commercially in communications and domestically, as in micro-ovens, increases the hazard of exposure to microwave. Increasing use of devices which are at risk from microwave, such as implanted cardiac pacemakers and metal surgical appliances and electronic monitoring devices in operating rooms and clinics, present increasing environmental hazards.*

THE FURTHER WE ADVANCE in scientific technology, the more hazardous we make our environment.

Eighty-six years ago Roentgen, Becquerel and Curie opened new vistas in discovering ionizing radiation in x-rays and uranium. The rays they discovered could not be seen, heard, felt or tasted. Gruesome indeed were the effects of this radiation upon the early disciples of this branch of physics. There were mutilating burns with resultant amputations of fingers, hands, arms; horrible, grotesque burn scars of the face, and for some a dismal degeneration to death. Among these victims were research physicists, technicians, physicians, radium dial painters—and even cancer patients for whom this new medium was intended as a cure.

Thirty years ago, early in World War II, a great deal of attention became focused upon another segment of the electromagnetic spectrum—specifically, radar. It should be emphasized that the energies produced in this range of frequencies are *non-ionizing.* Most of the physiological effects of radar, or microwave (MW) are thermal. Nevertheless, suspicion of a possible non-thermal pathological effect has stimulated considerable research in this field, but there is still great confusion and doubt as to what amount of microwave is safe or tolerable for humans—and for electronic devices, such as pacemakers, monitors and electrocardiographs, as well.

Microwaves are electromagnetic radiations, similar to ultra-violet, light, radio and infra-red rays which occur in the electromagnetic spectrum between radio waves and infra-red waves. The frequency range is from 30 to 300,000 megacycles per second and the length is from 1000 to 1 cm. They may be pulsed or continuous and are measured in watts or milliwatts.[1] They are of low energy value—for example, 1000 electron volts—and therefore are non-ionizing. They are produced by klystrons, fed through wave guides

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to antennae and then broadcast into the atmosphere. Microwaves are used in radiotelegraphy, radio broadcasting, radio communication, radar, wave guide transmission systems (long distance telephone), diathermy, and radio frequency furnaces. Radar is used to detect storms, guide and detect aircraft and missiles, detect traffic violators, and navigate ships and aircraft. The danger area around big tracking antennae is just about 500 feet, around microwave ovens only a foot; and it is negligible around telephone relays because the power is low. The range of danger around BMEWS* tracking radars is 2.8 miles and around NIKE sites 1000 feet.[2] The weather detection radar in the nose of aircraft might be a hazard to ground crews and repairmen if power is not turned off.

Experiments on Unicellular Organisms

In 1809 D'Arsonval observed that electric currents of 10,000 cycles per second produced heating effects. In 1935 up to 10 megacycles were developed and applied to diathermy. Currently, radars employing 10,000 megacycles and 10 million watts peak power are in use. In 1940 Everding, a Dutch physician, thought he could control the growth of experimentally produced tumors by injecting materials irradiated with microwaves. Little more was done until 1960 when, at the U.S. Army Medical Research Laboratory, Fort Knox, it was found that radio-frequency (RF) produced measurable changes in the optical polarity of glycogen in the hearts of chick embryos. In the U.S.S.R. Gordon, using 5 to 10 megacycles per square centimeter of RF on the isolated nerve of a dog, showed diminished transmission of stimuli in such a nerve after irridation. Microscopic examination of the nerve revealed globular accumulations of acetylcholine in the nerve. Other research projects with RF have dealt with acceleration of enzyme systems: changes in protein structure; changes in molecular weights of human blood constituents; determination of the amount of chemically bound water in serum; on size and weight of protein molecules; and investigation of cell membranes and cell contents.

Evidence of non-thermal effect of RF may be seen in the "pearl chain" formation when a suspension of polystyrene spherules of about one micron diameter are irradiated below a heat-producing field of 26 megacycles. Parameciae are seen to spin about their long axes with great velocity. When irradiated with RF at 100 megacycles, Euglenae irradiated in a 5 megacycle field go onto an east-west axis, but in a 6 megacycle field go onto a north-south axis. Amoebae, which usually are spheroid in shape, become ellipsoidal in shape with the long axis parallel to the field. Increasing the field strength disrupts the sphere, and the cell contents go into "pearl chain" formation. Some amoebae with pseudopods have the extensions split off, to spin along the sides of the parent body. Changing field strength from 5 to 27 megacycles causes the amoeba body to rotate 90 degrees, but cell contents remain in their original orientation. These phenomena are thought to be due to electromotive forces in the non-aqueous surface films of cells; this may open new avenues to the study of cellular and intracellular physiology.

Physiological Effects on Animals and Humans

Microwaves can affect multicellular organisms also. The factors influencing the exposure and absorption of microwaves by humans and other animals are numerous. Among the factors are the frequency and wave length generated by the equipment; the period of time of exposure; irradiation cycle rate; the on-off periods per unit of time; ambient air currents; ambient temperatures, body weight, type, mass, area, and covering; orientation of the body in the field, resonant conditions and standing waves inside the body; sensitivity of organs and tissues; reflections of waves and standing waves outside the body; absorption capacity of body fluids and tissues; and the capability to dissipate heat, primarily by blood flow.[5]

The balance between absorption and dissipation of heat by the human body is critical. It has been estimated that the human body can dissipate one kilowatt of absorbed power. This is less than the amount of power incident on a man lying prone in the noonday sun at the equator.[11] Whole body radiation with microwave to produce one degree rise in body temperature would cause a 5 to 14 percent rise in basal metabolic rate, which could produce a 50 to 100 percent increase in oxygen requirement, a reduction in oxygen transport by hemoglobin, and in turn a reduction in oxygenation in the pulmonary alveoli. The relative hypoxia would produce an increase of the affinity of the hemoglobin for oxygen at the tissue level. A reduction in the amount of oxygen available to tissues can lead to cellular death. The hypoxia can increase human fatigue and reduce efficiency. Temperatures within the body may increase to critical levels without warning because of lack of internal sensors. Internal organ heating can occur before an increase in body temperature can be detected either orally or rectally. Thus, enzyme and protein denaturization may occur before detection by conventional external measurement. Standing waves inside the body may produce an energy level higher than that incident at the body surface. Animal and plant experiments have demonstrated this specific thermal effect. Plants heated to the same temperature by infrared and by microwave were killed by the microwave heating. Rats, heated to 43°C by microwave died, but had to be heated to 47°C before they were killed by infra-red heating.

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*Ballistic Missile Early Warning System.

The absorption and penetration of the human body by microwave depends upon the wave length. To the longer waves the body is transparent, but the shorter waves are absorbed on the skin surface. If an absorbable wave is parallel to the body axis, three times more absorption can occur than if wave incidence is perpendicular to the body axis.[14] The human body can dissipate heat at the rate of 10 milliwatts to 100 milliwatts per square centimeter of body surface. Or, it can maintain heat equilibrium while absorbing 100,000 milliwatts to 1,000,000 milliwatts, the equivalent of 100 to 1000 watts of energy from an outside source. Once equilibrium is broken, fever occurs. If body temperature exceeds a rise of 5 degrees centigrade, death is likely. The two RF bands used most frequently are the S or 10 centimeter and X or 3 centimeter band. Irradiation from X band is absorbed at skin surface, and gives warning by heating effect. The S band waves penetrate and may be absorbed internally. If the heat cannot be dissipated because of poor blood circulation, it can produce tissue damage. In terms of frequencies, 10,000 megacycles per second waves are all absorbed at the skin; below 1000 megacycles per second waves are absorbed and may produce heat in deep tissues. The eyes are particularly vulnerable; cataracts may result. The testicles are heat-sensitive, and overheating can produce temporary sterility. The gall bladder, urinary bladder, and intestinal lumen may develop higher temperatures than the total body temperature. In small animals changes have been produced by using 10,000 times the dose considered safe for humans. Using 12 cm waves on rats has produced severe testicular damage; in rabbits exposure to 100 watts with 5 cm wavelength for 15 minutes has produced cataracts. If the dose of microwave for whole body irradiation is given in divided doses, it is less noxious. The absorption of microwave, and hence its effects, depends upon many variables, as summarized in Table 1.

TABLE 1.—***Effects of RF Energy on Man and Animals***

I. THERMAL EFFECTS	
HEAT SUPPLY	*AFFECTED BY*
RF energy	Frequency, power, time and space distribution
Metabolism	Body temperature
HEAT DISTRIBUTION	
Conduction	Temperature gradients
Blood Circulation	Many internal factors
HEAT REMOVAL	
Conduction Convection Radiation Evaporation	Body temperature, skin circulators, environmental temp., air speed, humidity, clothing
WHOLE BODY HEATING	Increased temperature with systemic readjustments
EYE	Lens opacities
TESTICLES	Sterilization
SKIN	Burns
II. NON-THERMAL FIELD EFFECTS	
Dipole Orientation	
Forces on dielectrics due to field gradient	
High frequency ion mobility	
Intense field-wien effect	
III. UNDETERMINED	
Increased relative effectiveness of pulsed fields	
Localized neurological effects	
Genetic damage to cells, etc.	

Lest we become over-anxious about the effects of microwave upon humans, it should be emphasized that there is no authentic record of a fatal injury from radar. There are some reports of eye damage possibly due to microwave radiation. In 1952, a 20-year-old radar repairman and a 32-year-old male electronics technician tested whether a microwave generator was working by sticking their hands into the beam or by looking into an invisible beam. Supposedly, they developed cataracts and choroiditis, but the evidence is circumstantial. On the other hand, Zaret reporting on a survey of 1000 microwave operators, found that only 42 showed pathognomonic signs of microwave damages, viz. posterior capsular opacification. Where the permissible exposure limit of 20 milliwatts per square centimeter in the occupational environment was enforced, no case of microwave cataract has been reported.[16]

In 1957, McLaughlin[9] reported fatality in a 42-year-old man who stood in a radar beam for less than a minute. Autopsy proved that the patient died of a ruptured appendix; and it is doubted that the amount of radar exposure was an etiological factor. A 58-year-old carpenter who had had a steel plate inserted into his left index finger worked with a diathermy machine which was used to dry glue on lumber. When he got his hand into the diathermy field, he had pain and swelling from the heat absorbed by the metal plate. A 31-year-old repairman who worked at a radar weather station, performed maintenance on radar antenna while the radar was operating and did not wear protective clothing. Testicular biopsy showed tubular atrophy, necrosis and cellular debris in tubular lumen. Rosenthal and Beering raised the question of biological damage in the case.[13]

Effects on Pacemakers

The increasing frequency of the use of implanted cardiac pacemakers has created a new risk from exposure to radar.[15] Fifty-five thousand implanted pacemakers are in use in this country. In 1965, Lichter demonstrated that some pacemakers in sheep or dogs' hearts could be accelerated and produce ventricular fibrillation if a microwave field irradiated certain types of pacemakers.[8] Surgical diathermy, physiotherapy diathermy, hyfrecators, radio transmitters and even neon advertising lights could trigger the pacemakers at a distance of six inches to two feet from the pacemaker. Pickers and Goldberg observed that a newly installed broadcasting station antenna 365 meters from the hospital confounded demand cardiac pacemakers and disrupted oscilloscopes, electrocardiographs and electroencephalographs in the cardiac surgery theatre; and on one occasion an electroencephalograph played "pop" music.[12] Electronically controlled heart lung pumps could be affected by RF. An implanted cardiac pacemaker in a 68-year-old physician caused him to have syncope and he became pulseless while at dinner in a restaurant. Later it was determined that he had been sitting near a microwave oven. Subsequently, while being monitored by an electrocardiogram, he was wheeled to within five feet of an operating microwave. High-frequency interference artifact appeared on the tracing and the doctor had transient symptoms.[7]

TABLE 2.—*Range of Effect of MW on Pacemakers**

Radar Station	158,400 cm
Radio Broadcasting Antenna	36,500 cm
Microwave Oven	150 cm
Diathermy Machine	30 cm
Lawnmower Sparkplugs	8 cm
Automobile Generator	6 cm

*As determined by various observers in various circumstances.

Acceleration of the rate of implanted cardiac pacemakers in dogs and sheep has occurred within 30 cm of a diathermy machine, 6 cm of an automobile generator and 8 cm away from the sparkplugs of a power lawnmower.[4] Cardiac defibrillators can disturb the function of implanted pacemakers, also.

Microwave ovens are being used in increasing numbers for domestic as well as commercial cooking; it is estimated that sales by 1976 will be 1,800,000 ovens. A survey of commercial ovens revealed a leakage of microwave in excess of 10 milliwatts per square centimeter in 20 percent of the ovens within 2 inches of the closed oven door. Leakage can occur with careless use of the oven or because of faulty hinges, gaskets, and safety locks or grease and dust around the door frame; or pitting of viewport plates from arc marks.[6]

Fire Hazards from Radar

There are other hazards in the use of microwave than exposure to the radar field. In highly powered radars if the generator uses more than 10 kilovolts, x-rays may be produced, and lead shielding is necessary. The electric power source may produce electroshock or fire, by short-circuits. Proper insulation and grounding procedures must be used. The radar beam can by induction ignite volatile vapors and fuels, metal wool, metal scraps, and the flash element in flash bulbs. Good housekeeping must be practiced. The sulfur hexafluorine in the wave guides may break down to sulfur and fluorine if arcing occurs. In some tubes, there may be residue of radium and radon gas. Tubes must be handled carefully to prevent breakage, and their storage area monitored for ionizing radiation.

Precautions in Using Diathermy, Microwave Ovens, Radar

The treatment for exposure to microwave is to prevent exposure to microwave. One should not enter an area of microwave radiation until all the transmitters are turned off and it is certain they will not be turned on again without notice. One should not look into an open wave guide. One should not climb poles or towers into the field of RF transmitters unless the power is off. Areas where radar is used should be monitored and unsafe areas marked with suitable warning signs. Proper sanitation and housekeeping must be practiced to keep flammable material out of radar beams. One should not test whether a radar generator is operating by feeling for heat or warmth as an indicator. Directional safety locks should be placed on scanning radars. Persons who must be exposed to radar in their work should wear goggles with wire mesh screening, and safety clothing made of material impregnated with animal hair, graphite, rubber and wire mesh. Radar generators should have interlocks to keep people out while the generators are operating. Antennae should be limited in their range of deflection or rotation to avoid directing the beam where vulnerable persons or apparatus may be working. Radar not fed into an antenna should be discharged into "dummy loads" and not dumped into closed areas. Domestic and commercial cooking ovens should be monitored, and their manufacturers and repairmen should be licensed. Users must be warned to operate these devices carefully. Hospital administrators, operating room supervisors, hospital staff members, and safety engineers should be alerted to the risk of exposing electronic devices—pacemakers, monitors, electrocardiographs, and cardio-respiratory pumps and the like—to a microwave field. Physicians must select properly shielded pacemakers and must educate their patients who use implanted electronic devices to beware of microwave ovens, radio transmitters, diathermy machines, dessicating devices, cardiac defibrillators, auto engines, power lawnmowers, and aircraft radars.

Persons employed in the production or use of microwave should have pre-employment physical examinations and periodic health evaluations. They should be asked about previous exposure to non-ionizing and ionizing radiation, laser beams, and infra-red radiation. If diabetes mellitus is present the fact should be recorded and note should be made of the presence and the site of any metal plates, pins or pacemakers.

In summary, lethal effects of microwave-radar have been documented only in experimentation with animals. Considering that in a quarter of a century of use there has been much exposure of humans to this form of energy, it is remarkable that lethal effects have not been documented.[3,10] It is remarkable, too, that so few non-lethal effects have been proved. Most of these effects are related to ocular lens damage. As the use of microwave becomes more common and as RF increases in power, vigilance and caution against this odorless, tasteless, soundless, invisible energy medium must be maintained.

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Medical Progress

The Problem of Chronic Inflammatory Bowel Disease

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ON THE BASIS OF CERTAIN clinical and histopathological features two distinct forms of chronic inflammatory bowel disease are recognized. In the absence of an understanding of their causes, the validity of this separation cannot be assessed from an etiological point of view. Its utility derives instead from histological appearances and clinical events which reflect different patterns of morbidity and mortality. The terms *ulcerative colitis* and *Crohn's disease,* although not wholly satisfactory, do have the advantage of convention and will be used here. Since Crohn's disease in its classic and most frequent form involves the small intestine, retention of the eponym preserves its unity regardless of anatomic distribution. Other designations are in frequent use, each emphasizing a particular feature of the respective condition. Thus, ulcerative colitis may be referred to as non-specific ulcerative colitis, proctocolitis, ulcerative proctitis, or mucosal colitis and Crohn's disease may be termed regional enteritis, regional ileitis, terminal ileitis, granulomatous enteritis, granulomatous ileitis, granulomatous colitis, enterocolitis or transmural colitis.

This separation into two seemingly distinct conditions should not obscure their obvious interrelationship which is expressed most fully in the colon where the distinction between ulcerative and granulomatous colitis at times may not be possible.

Both ulcerative colitis and Crohn's disease have occupied a significant place in recent medical literature. Despite this interest efforts to understand their cause have been unrewarding, management largely unsatisfactory, and morbidity and mortality discouragingly high. This is mainly due to our collective ignorance. In addition, however, misconceptions concerning diagnosis and management perist, thereby adding to the sense of futility with which the physician too often approaches these patients.

This discussion will present an overview of both disorders, emphasizing recent developments and concentrating on those aspects of both which continue to present major problems to the physician and surgeon.

Ulcerative Colitis

Pathogenesis

Ulcerative colitis appears most frequently in Great Britain where an incidence of 5 per 100,000 population at risk and a prevalence of 80 per 100,000 have been reported.[1,2] In North America, New Zealand and Australia, prevalence is probably about one-half that rate. Nonetheless, ulcerative colitis has world-wide distribution as evidenced by the reports emanating from places such as Costa Rica, Africa, India and the Bedouin Arabs. The higher incidence among Jews and the relative rarity among Negroes suggest ethnic factors but available evidence fails to distinguish between genetic and environmental influences. The same problem attends the

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familial aggregation of cases, which is on the order of 5 percent.[3,4] It is of interest in this respect that the familial incidence of both Crohn's disease and ulcerative colitis is interdependent. Furthermore, healthy relatives of patients more frequently possess antinuclear antibodies[5] and antibodies to colonic antigens as well as antigens derived from Escherichia coli 014.[6] Although a genetic predisposition remains unproved, available evidence points strongly in this direction. Of equally unknown significance is the age of onset which demonstrates a bimodal distribution with the greatest incidence in the second and third decades and a second smaller peak in the sixth decade.

Efforts to determine etiologic factors have tended to pursue a simplistic single cause approach, emphasizing infectious, psychogenic, or immunological processes. It is perhaps time this was abandoned and a multi-factorial origin examined.

Microbiologic studies involving various bacteria, including L forms as well as viruses, have demonstrated no departure from normal, and infection in the usual sense does not seem a likely cause.

The potential influence of psychogenic factors probably has been overemphasized. It is widely held that patients with ulcerative colitis are of a characteristic personality type. Finch's description is typical:[7] "The adult with ulcerative colitis is an obsessive-compulsive character with guarded affectivity. He is immature with a pseudomature veneer and petulant infantilism. He has difficulty in effectively expressing aggression, a hypersensitivity, a marked use of denial, disturbed object relationships with inadequate sexual identification and depressive trends." Finch describes the child with ulcerative colitis as being a rigid, perfectionistic "little old man" with neurotic, obsessive adjustment and an "obnoxious manipulator" who uses his illness as a means of dealing with the environment. This image is largely anecdotal, however, and the few controlled studies available fail to demonstrate a relationship between ulcerative colitis and personality type.[8,9]

Although serum concentrations of IgG, IgA, and IgM are generally normal, antibodies to a colonic epithelial cell antigen have been demonstrated, especially in children with ulcerative colitis.[10,11] These antibodies are heterogeneous, possessing both Kappa and Lambda light chains and Alpha, Mu or Gamma heavy chains.[12] In one study, 25 percent of IgA antibodies were of the secretory type.[12] No anticolon antibodies of classes IgD or IgE have been demonstrated. The titer of these antibodies bears no relationship to disease activity and they tend to persist after proctocolectomy. They have also been detected in patients with other disorders and in normal persons although in lower titer and less frequently. *In vitro* studies have shown them not to be cytotoxic for allogenic colon epithelial cells.[13]

Germ-free rat colon, human colon, E. coli 014 and other enterobacteriaciae contain common antigens.[14] Antibodies reacting with this heterogenetic antigen are also present more frequently and in higher titers in the sera of patients with ulcerative colitis but are by no means limited to this condition. More recently antibacterial antibodies have been found in the recto-colonic mucosa of patients with ulcerative colitis.[15] These tissue antibodies react only with certain fecal anerobes whereas serum antibodies from the same patients react only with fecal aerobes. The tissue antibodies are largely of the IgG type and are also found in a few normal persons. To what extent the anticolon and antibacterial antibodies overlap is not clear. Their frequency in unaffected relatives argues against their being simply a result of mucosal inflammation, but whether they are causally important or only a concurrent reflection of an altered immune state remains to be determined. Of perhaps more potential significance is the finding that circulating lymphocytes from patients with ulcerative colitis or Crohn's disease are cytotoxic for allogenic colon epithelial cells.[16-18] This effect has a remarkable tissue and disease specificity, persisting during clinical remission but disappearing by ten days after proctocolectomy.[19,20] It can be blocked *in vitro* by antilymphocyte serum and anti-IgM antibodies. It can also be blocked by previous incubation of the lymphocytes with a lipopolysaccharide from E. coli 019:B14, or serum from another but not the same patient with ulcerative or granulomatous colitis.[20] Conversely, previous exposure of the epithelial cells to anti-epithelial cell antibodies also prevents this cytotoxic effect.[16] Cytotoxicity can also be induced in normal lymphocytes by previous incubation with either

E. coli extract or serum from a patient with colitis. Shorter et al[21] have demonstrated the serum constituent conferring cytotoxicity to be contained in the IgM fraction.

This effect of small lymphocytes suggests a cellular sensitivity reaction involving bacterial antigens. Yet studies employing lymphocyte transformation, an *in vitro* correlate of cellular sensitivity, have been negative when either tissue or bacterial antigens have been employed.[22-24] Another *in vitro* correlate of cellular sensitivity reactions, the inhibition of the migration of peripheral leukocytes, has been studied by Bendixen.[25] He found inhibition in patients with ulcerative colitis but not Crohn's disease with either colonic or jejuno-ileal homogenates. No evidence for an immunological defect of the type seen in Crohn's disease has been presented.

Whether reactions involving serum antibodies or small lymphocytes and tissue or bacterial antigens are involved in the mucosal inflammation remains unknown. The evidence thus far is encouraging, however, and at present this approach appears to be the most promising avenue of investigation.

Clinical and Pathological Features

Although ulcerative colitis is primarily a disorder of the colon, it is increasingly clear that it is often a systemic disease with a wide range of extracolonic manifestations. The colon's contribution to the clinical picture is in the form of some combination of diarrhea, hematochezia, and cramping lower abdominal pain. The intensity of these symptoms varies widely between patients and from time to time in the same patient. Onset may be gradual or fulminant and the course chronic and continuous or remittant and relapsing. Asymptomatic intervals vary from a few weeks to many years but once the disease has occurred eventual relapse is the rule, the rate varying between 27 and 50 percent per year.[26,27] Fever and minor degrees of leukocytosis are common, especially during more severe attacks. Anemia is common and is most often due to blood loss which is largely occult. Other causes of anemia include malabsorption of iron, autoimmune hemolytic anemia,[28] microangiopathic hemolytic anemia,[29] G-6-PD deficiency,[30] and Heinz body anemia caused by salicylazosulfapyridine (Azulfidine).

Abdominal examination in an uncomplicated case exhibits only varying degrees of diffuse tenderness. The presence of rebound tenderness in the absence of guarding does not necessarily indicate perforation and peritonitis. It may only reflect sudden stretching of an inflamed bowel wall. Sigmoidoscopy is mandatory to the diagnosis and there is never a contraindication to performing at least a limited examination. In the presence of severe diarrhea and bleeding the examination should be attempted without preparation. If preparation is required a Fleet® enema is adequate and safe. Classically the mucosa appears hyperemic, edematous, granular, friable, often with fine ulcerations and active bleeding. Involvement is always continuous, never discontinuous over the length involved. The only reproducible observation between even experienced sigmoidoscopists is friability. It should be noted that bleeding induced by a suction tip or the sigmoidoscope itself may not be reflective of any abnormality. Abrasion with a cotton swab is a more reliable indication of true friability. The mucosa may appear macroscopically normal with mild disease or at best equivocally abnormal.

It is in this situation that rectal biopsy has its greatest value. It is commonly stated that the rectum is abnormal in at least 95 percent of patients with ulcerative colitis, but in point of fact if disease is present elsewhere in the colon a histologically normal rectal biopsy virtually excludes the diagnosis of ulcerative colitis. During complete remission, however, the histological appearance may revert to normal.

Anal and perianal lesions occur in approximately 10 percent of patients and consist of midline dorsal fissures, excoriation of the perianal skin, perianal and ischiorectal abscesses and rarely recto-vaginal fistulae.[31] Spontaneous enterocutaneous fistulae are virtually never seen in patients with ulcerative colitis. In contrast to Crohn's disease anal lesions occur only after the onset of the proctocolitis. During the subsequent discussion of Crohn's disease it will be seen that anal lesions constitute an important differential diagnostic feature between these two disorders.

Ulcerative colitis characteristically spreads proximally in a continuous fashion, never with "skip areas" and with a gradual merging with normal bowel. In a small proportion of patients disease remains limited to the rectum or the rectum and very distal sigmoid colon. The term *ulcerative proctitis* has been used for these patients. Histopathologically it is not different from the more generalized disease, but the manifestations are generally mild and the prognosis good. One cannot predict, however, which patients will continue to have localized disease. There is no reason to consider this form anything other than "ulcerative colitis" limited to the rectum.

The histological appearance of ulcerative colitis is not pathognomonic.[31] None of the individual components of the reaction are specific. It is the overall pattern of response that is characteristic. The most pronounced changes are always present in the mucosa. In the presence of active disease there is mucosal capillary dilatation and hemorrhage, epithelial cell necrosis, goblet cell depletion, crypt abscesses, rather broad ulcerations, and infiltration of the lamina propria with lymphocytes and plasma cells with much less in the way of neutrophilic and eosinophilic leukocytes. The submucosa shows very little change except when ulcers extend into it, and lymphoid hyperplasia is limited to the mucosa and superficial submucosa. Although crypt abscesses are considered a hallmark of ulcerative colitis, they are also seen in granulomatous colitis, Shigellosis, amebiasis, and radiation proctitis. As the disease becomes more chronic, the appearance is one of mucosal atrophy, reactive epithelial hyperplasia, loss of goblet cells, lymphocytes and plasma cells in the lamina propria and paneth cell metaplasia at the base of the crypts. It is both interesting and important that there is little or no fibrosis even in the presence of chronic disease.

The terminal ileum is superficially inflamed in approximately 10 percent of patients and always in contiguity with disease in the cecum and ascending colon. This has been termed "backwash ileitis." More proximally peroral aspiration biopsy of the jejunum or ileum sometimes shows partial villous atrophy which in some patients may explain the associated lactase deficiency and mild absorptive defects.

The radiologic appearance of ulcerative colitis is well known and only a few points require emphasis. Barium enema studies are helpful in establishing a diagnosis and in determining the extent of disease. Radiologic information should not be used to dictate therapy except for the fact that the presence of total involvement constitutes one factor influencing the risk of carcinoma. It is the appearance of the patient not his colon that is important. This point receives emphasis from the demonstrated variation between observers in the interpretation of barium enemas.[32] The examination should not be undertaken in a seriously ill patient especially if signs suggesting toxic megacolon have supervened. If the diagnosis has been established by sigmoidoscopy and specific infections or infestations excluded, colectomy, if justified, may be performed without radiologic examination. Such a patient will invariably show total or near total disease and the barium enema will not be helpful but potentially hazardous. More important than the mere introduction of barium, however, is the method of preparation. In patients with severe diarrhea but otherwise not critically ill, the barium enema may be attempted without any preparation and the results, though not the best, will usually be adequate. When preparation is required a safe and effective method consists of a liquid diet for 24 to 48 hours followed by oral magnesium citrate. The use of castor oil and irritating suppositories should be discouraged.

The majority of radiologic abnormalities in patients with ulcerative colitis are potentially reversible. The shortening, narrowing and loss of haustrations are not due to fibrosis but to muscle contracture and are fully reversible in some patients. Strictures are unusual and any localized area of constant narrowing is highly suspicious of carcinoma. When benign strictures do occur, they are more often due to thickening of the muscularis mucosa than to fibrosis.[33] The greatest difficulty from a radiologic point of view is the differentiation of ulcerative from granulomatous colitis. This problem will be discussed in connection with Crohn's disease.

The use of periodic barium enema examinations to detect carcinomas has not been proved to have clinical value with regard to prognosis. Such an approach has more to offer the physician than the patient.

The extracolonic manifestations of ulcerative colitis fall into two groups; those that appear to be secondary to the colitis and those that pursue an independent course. The former may to some extent parallel the clinical severity of the colitis but most importantly usually disappear after total coloproctectomy. The latter are uninfluenced either by the state of the colitis or the removal

TABLE 1.—*Extracolonic Manifestations of Ulcerative Colitis*

Lesions	*Affected by Operation*
Skin lesions[34,35]	
Erythema nodosum	yes
Erythema multiforme	yes
Pyoderma gangrenosum	yes
Nonspecific pustular dermatosis	yes
Mucous membrane lesions[36,37]	
Aphthous stomatitis	yes
Ulcerative esophagitis	?
Eye lesions[38,39]	
Episcleritis	yes
Uveitis	yes
Iritis	yes
Conjunctivitis	yes
Marginal corneal ulceration	yes
Bone and joint lesions[40,41]	
Arthralgias	yes
Sacroiliitis	no
Arthritis of ulcerative colitis	yes
Ankylosing spondylitis	no
Rheumatoid arthritis	no
Hepatobiliary lesions[42-47]	
Active chronic hepatitis	no
Pericholangitis	no
Unclassified inflammatory changes	possibly
Cirrhosis (postnecrotic and biliary)	no
Carcinoma of extrahepatic bile ducts	no
Primary sclerosing cholangitis	no
Pericarditis[48]	?
Renal calculi[49]	?

of the diseased colon. Although rarely themselves indications for surgical operations this is important to bear in mind when detailing the hoped-for benefits of colectomy to the patient. None of these conditions are specific for ulcerative colitis and most are encountered in patients with Crohn's disease, especially when it involves the colon.

The extracolonic lesions and other associated disorders encountered in patients with ulcerative colitis are summarized in Table 1. The hepatic lesions deserve special comment because they have the greatest influence on prognosis. The presence of fatty infiltration is a direct consequence of nutritional disturbances and not directly related to the colitis. Of concern are the types of inflammatory changes encountered. Eade examined 132 biopsy specimens of consecutive patients coming to colectomy.[42] Although the quantitative aspects of this study are no doubt skewed in favor of severity, the qualitative relationships are probably applicable to patients with ulcerative colitis in general. Seventy-three percent exhibited some inflammatory change. Of this group, 24 percent showed inflammatory cells only, 40 percent had both inflammatory cells and increased fibrosis, and 36 percent fibrosis only. Bile duct proliferation and hepatic cell necrosis were always associated with inflammatory cells, with or without fibrosis.

The important question is whether any discrete entities are contained within these abnormalities. In some it is possible to arrive at a diagnosis of active chronic hepatitis and in others to classify the lesion as pericholangitis. There is no agreement on the nature or significance of the remainder. Some may resolve, others eventuate in one of the conditions mentioned above or simply persist unchanged. Active chronic hepatitis (lupoid hepatitis, juvenile cirrhosis, plasma cell hepatitis, hypergammaglobulinemic hepatitis of Waldenstrom, Kunkel girls) has about an 80 percent chance of progressing to postnecrotic cirrhosis and eventually death from liver disease. In such patients prognosis is more closely related to the liver disease than the colitis, and elective colectomy is probably unwise in the majority. The term *pericholangitis* is in part a misnomer since the inflammatory change is more closely related to the portal vein than to the bile ducts. The patients exhibit rather pronounced elevation of alkaline phosphatase, 5′ nucleotidase or leucine aminopeptidase with relatively minor changes in the serum bilirubin. In many cases the lesions will resolve completely while some will progress to biliary cirrhosis.[45] Eade et al suggested that colectomy has a beneficial effect on the various inflammatory changes.[43] This may be true for the relatively minor and non-specific changes but there is no evidence that the course of active chronic hepatitis, cirrhosis and pericholangitis is materially affected.

Complications, Prognosis and Management

As the complications, prognosis and management of ulcerative colitis are related, they will be discussed together. True complications represent direct and obvious consequences of the inflammation in the colon and are therefore of a different character than the extracolonic manifestations already discussed. These complications include severe hemorrhage, free perforation, toxic megacolon and carcinoma. Obstruction and fistulization are rare in patients with ulcerative colitis. The problem of hemorrhage is rather straightforward and needs little comment. Most often it subsides spontaneously, or possibly as a result of treatment, and seldom of itself is an indication for colectomy. Spontaneous perforation is most common during the first attack in a patient with extensive involvement, and most frequently occurs in the sigmoid colon. Treatment is surgical.

Toxic megacolon is the most serious acute complication of ulcerative colitis, and recognition of it is made difficult by lack of a precise definition. It occurs in approximately 2 percent of all patients and 20 percent of those with fulminant attacks.[50] The patient appears quite ill with fever, bloody diarrhea, leukocytosis and abdominal distention. Frequent but less constant findings are anemia, hypoalbuminemia and a prolonged prothrombin time. The colonic dilatation is best appreciated on plain films of the abdomen, which should be obtained once or twice daily in every patient with a severe attack. The upper limit of normal for the diameter of the colon on plain films is 5.5 cm and on double contrast barium enemas 6.5 cm.[51] These measurements should be taken as a general guide, however, and always in conjunction with the clinical findings. The dilatation is most apparent in the transverse and sigmoid portions, probably for two reasons: the presence of a mesentery allowing these areas to more readily distend, and the fact that in the recumbant position these segments are more superiorly located. Many potential precipitating factors have been incriminated but in no case is the evidence persuasive. The entire thickness of the colon is involved with a severe inflammatory process and perforation is common. The pathophysiology of the condition remains obscure. Once the diagnosis has been made the treatment is surgical,[52] a decision that is reinforced by the fact that fully 80 percent of those surviving with medical management subsequently require colectomy for other reasons. The operation of choice is one-stage total proctocolectomy and ileostomy. Turnbull et al expressed the opinion that if one or more walled off abscesses are present the initial procedure should be limited to ileostomy and transverse colostomy, with colectomy carried out later.[53] Even with a vigorous surgical approach the mortality is in the range of 13 percent.[54] Toxic megacolon has also been known to complicate amebic colitis,[55] and this must always be borne in mind.

Carcinoma, on the other hand, represents the most serious late complication. Its overall incidence is in the range of 3 to 4 percent.[56,57] Three high risk factors can be identified.[58] They are the presence of total or near total colonic involvement, duration of disease for ten years or more, and onset before the age of 18. The risk increases progressively after ten years, and after 20 years of disease the annual increment of risk is 5 percent, to a cumulative incidence of 40 percent after 25 years. The tumors tend to be multicentric and traditionally the prognosis is poor. One recent report, however, describes a five-year survival of 40 percent, a figure comparable to that for other adenocarcinomas of the colon.[59] The manifestations of the tumor are often ascribed to the underlying colitis, which may cause delay in diagnosis. As has been pointed out, periodic barium enema examination has not proved of value for early detection, nor has colonic cytology. Pang and Morson[60] described precancerous histologic changes in rectal biopsy specimens, but further confirmation is required before this can serve as a basis for prophylactic colectomy. Periodic assays for the presence of carcinoembryonic antigen in a high risk patient's serum may prove useful.[61,62]

Fortunately the complications of severe hemorrhage, perforation, toxic megacolon and carcinoma, all best treated by operative means, affect a minority of patients. It is in the remaining patients, the majority, that the nature and place of medical and surgical management continues to be debated.

Although there is incomplete agreement on various factors affecting prognosis, certain guidelines do emerge from the studies at Oxford and Leeds.[26,63,64] Outcome is most dependent on the age of the patient, the extent of involvement and the severity of the current attack, mortality being highest in those above age 60, those with total involvement and those having the severest attacks. The single most important factor, however, is the severity of the attack. Severity tends to be greatest with the first attack, with total involvement, and in the very young and very old. The reported mortality for severe attacks varies between 11 and 26 percent, while that for mild or moderate attacks is less than 1 percent. Rapidity of onset also relates to mortality but primarily because it relates to severity.

The late outcome or long term mortality has been harder to define. Most studies are based on projected values involving relatively small numbers of patients. In the Leeds study patients with total involvement had an annual mortality of 2.7 percent with a cumulative expected mortality of around 40 percent after 25 years of disease. Jalan et al,[65] however, expressed belief that patients surviving the first referred attack without operation have a long term mortality little different from that of the general population.

The issue in reality resolves itself into two questions. What should be our approach to acute attacks, and when is elective colectomy indicated? All acute attacks regardless of severity and barring the previously discussed complications, should be medically treated initially. Medical management is symptomatic, supportive and largely empirical. No form of therapy now available has been shown to reduce the proportion of patients eventually requiring colectomy. Mild and most moderate attacks can be treated at least initially without admitting the patient to hospital. All severe attacks require inpatient management. At the very outset it is of paramount importance to thoroughly discuss the patient's disease with him; its possible course and prognosis, its management, including the future possibility of colectomy, and precisely what can and cannot be done. An informed patient will cope with his disease far better than one who is not.

Mild and moderate attacks will usually respond to rest, measures to control diarrhea, and the administration of Azulfidine. Useful approaches to the control of diarrhea include administration of diphenoxylate hydrochloride with atropine sulfate (Lomotil®), tolerance doses of belladonna, psyllium hydrophilic muciloid (Metamucil®) and aluminum hydroxide, and temporary reduction of oral intake. Azulfidine in doses of 2 to 8 grams daily has been proved effective for control of acute attacks and reduction of exacerbations, although its mode of action is not understood.[66,67] It should be continued in a maintenance dose of 2 grams daily for a minimum of several months after the attack has resolved. Whether it should be employed indefinitely is moot. If experience in the individual patient over a period of time demonstrates its value and relapses are frequent, continuous indefinite therapy may be useful. Patients should be maintained on a full general diet and advised to exclude only those foods which consistently cause more symptoms. A distinct minority of patients may benefit from a milk-free diet.[68] What proportion of such patients are lactase-deficient is not clear. The frequency of lactase deficiency in patients with ulcerative colitis is probably not increased.[69] If these measures fail to provide a satisfactory response, prednisone in an initial dose of 30 mg per day may be effective. It should be tapered and discontinued gradually over a period of two to three months. Corticosteroids, although effective in acute attacks, have no prophylactic value[70,71] and are less effective for chronic continuous disease and with repeated usage. Long-term maintenance therapy with oral steroids should not be employed. Steroid retention enemas may be useful, especially in distally located disease, but they have no advantage over short term oral therapy if the latter is successful. If long term therapy is to be tried, the periodic rectal administration of 100 mg of hydrocortisone in 120 ml of tepid tap water or saline solution by slow drip may prove beneficial. Goldberg et al[72] administered 50 mg of hydrocortisone alcohol in 2 ounces of safflower oil as a retention enema at bedtime with good results in children. Whether the course of the disease in whole is significantly modified by this form of therapy is not known.

The endpoint of medical treatment will not be the same in every patient. Some will have complete remission, but others will continue with varying degrees of symptoms despite all available therapy. When chronic continuous disease or the frequency of recurrent attacks leads to progressive nutritional deficits or significantly interferes with the patient's overall well-being and pattern of living, colectomy should be carried out. In the absence of any immediate threat to life, the patient is the best judge of when this should be done; and, lest the result be an unhappy patient with an ileostomy, he should be reasonably convinced of its necessity. He should also be made aware of the risk of carcinoma and consider this in his deliberations, but the final decision properly belongs to him.

Although dissenting opinions exist, the recommended procedure is one stage total proctocolectomy.[73-75] When done electively, this operation carries a mortality not exceeding 3 percent. Intractable symptoms with or without nutritional impairment continue to be the most frequent indication for colectomy. In a child with ulcerative colitis the eventual risk of carcinoma will be higher, and therefore even more weight should be given to this factor in considering the indications for colectomy in this age group. An additional consideration in children is the presence of growth retardation and failure of sexual development, which may in themselves be indications for colectomy even when daily symptoms are not particularly disabling. Despite some claims to the contrary,[76] diverting procedures and ileorectal anastomosis are seldom effective even as temporary measures and cannot be expected to reduce long term morbidity and mortality.[77,78]

Severe attacks require treatment in hospital. The patient should be examined at least twice daily and surgical consultation obtained at the very outset. Management initially consists of bed rest, mild sedation, nothing by mouth except for medications, intravenous fluids, correction of significant anemia, some combination of the previously mentioned measures to control diarrhea and Azulfidine 4 to 8 grams daily. Nasogastric suction is employed only if beginning dilatation of the colon is suspected. Systemic antibiotics should not be employed unless there are specific indications for them. In contrast to the situation in a case of mild or moderate disease, in dealing with severe attacks a given program must be dramatically effective within a short time or other measures must be instituted. Therefore if *significant* improvement has not occurred within four to five days, corticosteroids should be added. This is best accomplished by administering 200 mg of hydrocortisone intravenously each day. Some observers would institute all of these measures initially and not in the stepwise fashion described. The preference for withholding steroids at first is that many patients will respond to the more conservative measures and the necessity for them may be avoided. An exception is the patient who has required steroid therapy for previous attacks. It is doubtful that immediate use of them results in any higher remission rate than waiting four to five days to begin. Corticosteroids do not seem to influence the outcome of surgical treatment as to operative results, complications, wound healing or mortality.[79] Unless the patient has rather dramatic improvement after an additional four to five days, colectomy should be undertaken. The greatest danger in the management of severe attacks is procrastination. Although most studies place the operative mortality for emergency colectomy near 20 percent,[80,81] in more recent studies of cases in which operation is done earlier in severe attacks mortality has been reported at 2 to 10 percent.[82,83] In cases of acute onset and fulminant course it is vital that specific infections such as shigellosis and amebiasis be excluded. In acute disease, colectomy should not be done until stool cultures and adequate examinations for ova and parasites have been carried out.

The single most frequent reason for avoiding or delaying either elective or emergency colectomy in the patient with ulcerative colitis is the necessity for a permanent ileostomy. The morbidity and mortality of an ileostomy, however, do not compare with the morbidity and mortality of the disease for which it was carried out. Patient acceptance is generally quite good, provided the indications for ileostomy were valid in the first place. Improvements in the procedure by Brooke and Turnbull and the development of new appliances have greatly decreased management problems. Not more than 10 percent of patients with ulcerative colitis who have ileostomy will require surgical revision.[84] The figure for granulomatous colitis is higher, however, and the reasons for this will be discussed subsequently.

There is both an emotional and a rational approach to the treatment of patients with ulcerative colitis, and rational management is best carried out by the joint efforts of a surgically oriented physician and a medically oriented surgeon.

Crohn's Disease

Pathogenesis

Crohn's disease has an ethnic and age distribution similar to that of ulcerative colitis except for the lack of a secondary peak in the older age group and, as pointed out, a familial incidence that is interdependent with the latter. Reliable data on the incidence and prevalence in the general population and the geographic distribution are not available, however, owing largely to the uncertain frequency of granulomatous colitis and the fact that a firm diagnosis often requires surgical material. It has been regarded as occurring about half as frequently as ulcerative colitis but there is an undocumented belief by many that Crohn's disease, especially of the colon, is increasing in frequency, particularly in proportion to ulcerative colitis.[85,86] Again a genetic predisposition seems probable. An association between Crohn's disease and G-6-PD deficiency has been reported[87] and at least five sets of monozygotic twins with Crohn's disease have been described.[88] It is of interest that the age of onset and clinical course were remarkably similar in the members of each set. Compared with ulcerative colitis, investigation has until recently been rather desultory but now there is considerable interest in Crohn's disease from both an immunological and microbiological point of view.

Serum immunoglobulin levels are generally normal, but anticolon antibodies occur with a frequency similar to that for ulcerative colitis.[89,90] No antibodies reacting with small bowel have been demonstrated. Furthermore, Bendixen found no inhibition of peripheral leukocyte migration with jejuno-ileal homogenates.[25] Peripheral lymphocytes are cytotoxic for allogenic colon epithelial cells, exhibiting the same characteristics described earlier for ulcerative colitis. They are not, however, cytotoxic for ileal epithelial cells. A major point of difference from ulcerative colitis is the presence of anergy in a significant proportion of patients with Crohn's disease. Peripheral lymphocytes are hyporesponsive to phytohemagglutinin[91,92] and the ability to develop cutaneous sensitivity to 2,4 dinitrochlorobenzene is impaired.[93] This anergy and the granulomatous nature of the lesions have prompted a comparison with sarcoidosis. A positive Kveim reaction has been reported in approximately 50 percent of patients with Crohn's disease[94] and the migration of peripheral leukocytes from patients with either sarcoidosis or Crohn's disease is inhibited by Kveim antigen.[95]

An infectious process in the etiology of Crohn's disease also remains an attractive possibility and Golde has drawn an interesting analogy to leprosy.[96] Possible support has been provided by the demonstration of a transmissible "agent" by inoculating the footpads of mice with tissue from patients with Crohn's disease and producing a granulomatous reaction.[97] Evidence has also been presented that atypical mycobacteria are present in a lysogenous state in the lesions of sarcoidosis.[98] No increased frequency of dermal reactivity to atypical mycobacterial antigens has been found in patients with Crohn's disease, however.[99]

Psychogenic factors have received much less emphasis in Crohn's disease than in ulcerative colitis. McKegney et al[100] in a retrospective and prospective study could find no difference between ulcerative colitis and Crohn's disease with respect to demographic, psychosocial, personality, behavioral and psychiatric characteristics. The severity of the emotional disturbance tended to correlate with the severity of the physical illness. Similarly, Goldberg[101] could find no distinguishing personality types when comparing patients with nontropical sprue, Crohn's disease and alactasia.

The possibility that ulcerative colitis and Crohn's disease are etiologically related seems highly likely. It is equally obvious, however, that some very fundamental differences exist.

Clinical and Pathological Features

Although rarely described in the esophagus and stomach, Crohn's disease is most frequent in the small bowel and colon, with 50 to 66 percent occurring in the small bowel only, 10 to 17 percent in the colon alone, and 17 to 40 percent involving both (enterocolitis).[31,86] Ninety percent of small bowel disease occurs in the terminal ileum. In the colon, Crohn's disease in contrast to ulcerative colitis tends to be more proximally located, often being limited to the ascending colon and sparing the rectum in about 50 percent of patients. The term "right sided colitis" found in the older literature no doubt describes cases of granulomatous colitis, at the time unrecognized. When disease is limited to the colon a firm diagnosis often requires surgical material. Our estimate of the frequency of colonic involvement is therefore probably low, since many cases are diagnosed on clinical and radiological grounds as ulcerative colitis.

The gastrointestinal manifestations of Crohn's disease consist mainly of abdominal cramping pain and increased frequency of bowel movements. The type of urgent watery diarrhea often seen in patients with ulcerative colitis is seldom encountered in Crohn's disease except when there is rectal involvement. Gross blood in the stool is also infrequent, although significant occult losses are common. The clinical course of Crohn's disease is more persistent and indolent than that of ulcerative colitis, with little in the way of acute, severe attacks. Obstruction and fistulization are common and anal and perianal lesions are found in 25 percent of all patients and in 80 percent of those with involvement of the large bowel.[102,103] They take the form of indolent, undermined anal fissures anywhere in the anal canal, sometimes extending to involve extensive areas of the perineum and even inguinal regions,[104] enterocutaneous fistulae, solitary ulcers and edematous anal tags. Anal lesions at times are the initial manifestation of disease, and biopsy of an ulcer, fissure or fistulous tract may demonstrate granulomas and greatly assist in diagnosis.

Nutritional disturbances including weight loss, anemia, hypoproteinemia, electrolyte depletion and vitamin deficiencies are common and may dominate the clinical course. Weight loss is largely due to poor intake because of abdominal pain and anorexia although steatorrhea may contribute. Malabsorption of fat may be secondary to mucosal involvement, resection (short bowel) and bile salt depletion or deconjugation from bacterial overgrowth. Hypoproteinemia results from enteric loss compounded by poor intake. The anemia is most commonly iron-deficient due to occult blood loss, but folic acid and B_{12} deficiency are also frequently present. Concomitant marrow depression of uncertain cause may contribute to the anemia and to suboptimal response to specific therapy. It is evident that the successful management of nutritional deficiencies must be based primarily on amelioration or elimination of the basic inflammatory process in the bowel.

Sigmoidoscopic appearance is variable. As was previously noted, about half of patients with large bowel involvement and all patients with disease limited to the small bowel have a normal rectum. In the known presence of more proximal disease, this in itself strongly favors a diagnosis of Crohn's disease. In a small proportion of patients with rectal involvement the lesion will not be macroscopically distinguishable from ulcerative colitis. In the remainder there are features suggesting the presence of Crohn's disease. These include skip areas, large ulcerations, and the anal and perianal lesions described above. In Crohn's disease, unlike ulcerative colitis, the demarcation between normal and abnormal bowel is relatively sharp. Opinions differ regarding the usefulness of rectal biopsy in establishing the diagnosis. As will be discussed, the major thrust of the disease is in the submucosa and a biopsy specimen to be helpful must be deep enough to include a goodly portion of this area. Such a specimen can be safely taken only on the rectal valves or the margin of an ulcer. If characteristic changes are observed, a diagnosis of Crohn's disease should be considered likely. If not, a differential diagnosis is best not made on the histological material.

TABLE 2.—***Pathological Features of Ulcerative Colitis and Crohn's Disease***

	Crohn's Disease	*Ulcerative Colitis*
	GROSS	
Anal and perianal lesions	major & common	minor & uncommon
Bowel wall	thickened	normal—slight increase
Strictures	common	uncommon
Fistulae	common	rare
Pseudopolyps	rare	common
Ulcers	"fissure"	punctate to trough-like
Distribution	more proximal	more distal
Continuity	often "skip" areas	always contiguous
Toxic megacolon	uncommon	more common
Carcinoma	rare	increased
	MICROSCOPIC	
Primary impact	submucosa	mucosa
Type of reaction	productive	exudative
Lymphoreticular hyperplasia	marked & transmural	minimal & superficial
Granulomata	40-80%	occasionally
Crypt abscesses	occasionally	usual
Vascular ectasia & edema	marked	related to acute inflammation
Epithelial regeneration	rare	common

Whereas ulcerative colitis is mainly a mucosal inflammation, Crohn's disease has its greatest effect at least initially on the submucosa, with gradual extension to transmural involvement. The degree of mucosal abnormality is always less severe than that seen in the submucosa, which is thickened due to edema and fibrosis and exhibits lymphangiectasia and moderate numbers of mononuclear cells. Lymphoid hyperplasia is pronounced and is distributed transmurally. Granulomas are present in from 40 to 80 percent of specimens, depending largely on the diligence with which they are sought. Ulcerations are

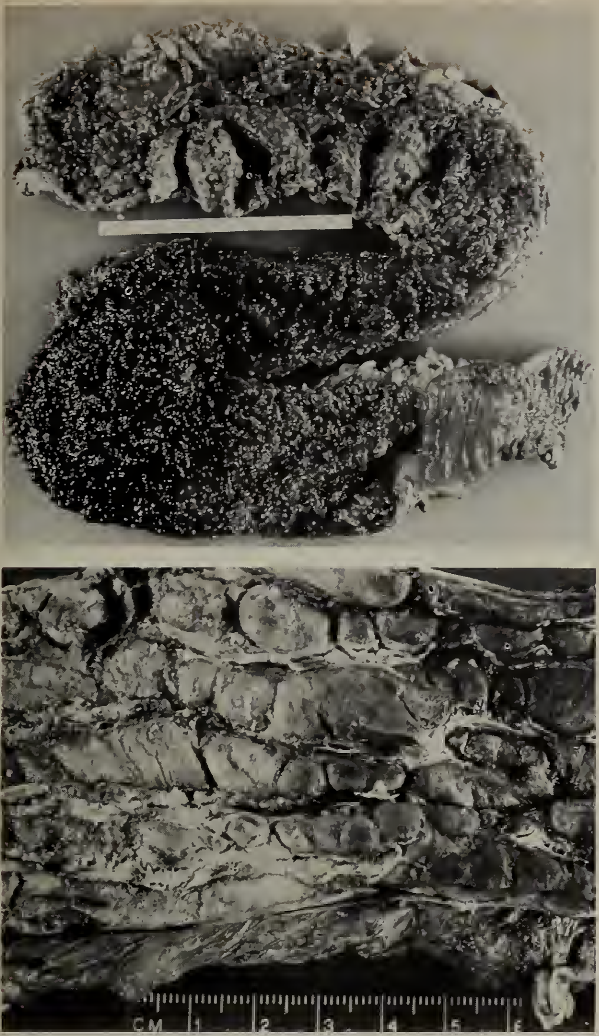

Figure 1.—*Upper*, gross appearances of ulcerative colitis. Note the relatively uniform involvement with diffuse ulceration and hemorrhage. *Lower*, gross appearance of a segment of colon involved by Crohn's disease. There are longitudinal and transverse-fissure ulcers intersecting to produce a cobblestone appearance.

either longitudinally or transversely oriented. The latter take the form of deep cleft-like fissures which have a characteristic radiologic appearance and are responsible for fistulization. The most reliable signs of Crohn's disease are sarcoid-like granulomas and fissuring. Granulomas are not pathognomonic, however, since they are occasionally found in otherwise classic ulcerative colitis. In contrast to ulcerative colitis it is doubtful that bowel involved by Crohn's disease ever reverts to an entirely normal appearance.

The histopathological characteristics of ulcerative colitis and Crohn's disease form the basis for most of the differences observed clinically and radiographically. These differential features are summarized in Table 2 and the gross appearances contrasted in Figure 1.

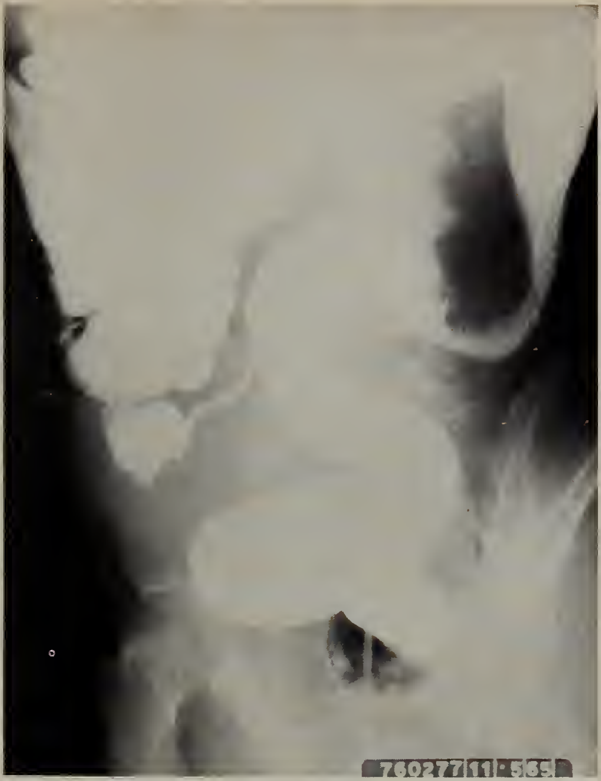

Figure 2.—Barium enema study illustrating segmental involvement of the descending colon by Crohn's disease.

The extra-intestinal manifestations are similar to those encountered in ulcerative colitis although their incidence is less well defined. They tend to occur less frequently, being most often encountered in the presence of granulomatous colitis.

Radiologic examinations provide the most certain means of diagnosis short of surgical resection. Barium studies should include both upper gastrointestinal and barium enema examinations in all patients. The former should provide a detailed small bowel study and the latter adequate spot films of the terminal ileum which is often best evaluated from below. The characteristic features of Crohn's disease involving the small bowel are well known and generally offer little difficulty in diagnosis. A major problem exists, however, in differentiating Crohn's disease of the colon from ulcerative colitis. Abnormalities characteristic of Crohn's disease and not seen in ulcerative colitis include segmental involvement (Figure 2), enteric fistulae, spike-like fissure ulcers (Figure 3), skip areas (Figure 4) and asym-

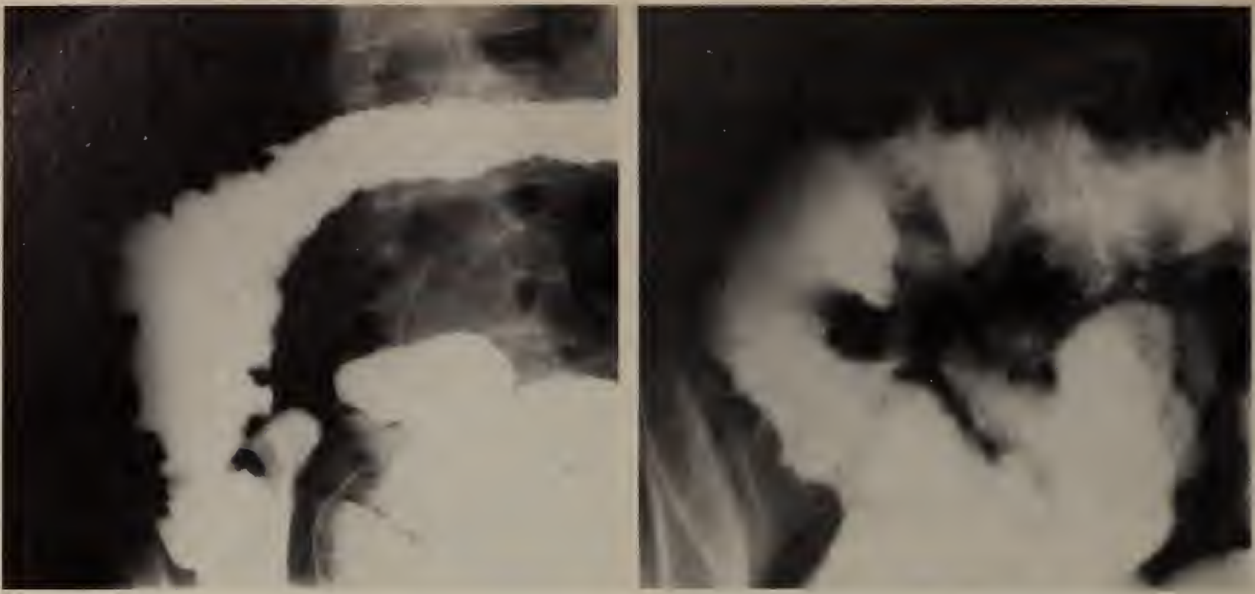

Figure 3.—*Left,* colon involved by Crohn's disease. Characteristic spike-like fissure ulcers are evident especially along the inferior margin of the transverse colon. *Right,* another example of fissure ulcers of the ascending and transverse colon in Crohn's disease.

metrical involvement of the bowel wall (Figure 5). A cobblestone appearance of the mucosa may be produced by the intersecting transverse and longitudinal ulcers, silhouetting the circumscribed edematous mucosa (Figure 4). A typical case of ulcerative colitis is illustrated in Figure 6. The "backwash ileitis" of ulcerative colitis should not cause confusion, since it produces only mucosal edema with loss of mucosal markings and dilatation, not narrowing, of the terminal ileum. The reversibility of radiologic changes in Crohn's disease is distinctly less than in ulcerative colitis but improvement may occur in ulcerations, fissures, cobblestoning and loss of haustral markings.[105] To the extent that narrowed areas are involved with spasm, they too may regress. Complete restoration to a normal radiographic appearance is highly unlikely, however. Selective angiography has not proved to be of particular value in distinguishing ulcerative and granulomatous colitis,[106] although at times it may be helpful in differentiating Crohn's disease in the small bowel from lymphoma and other tumors.

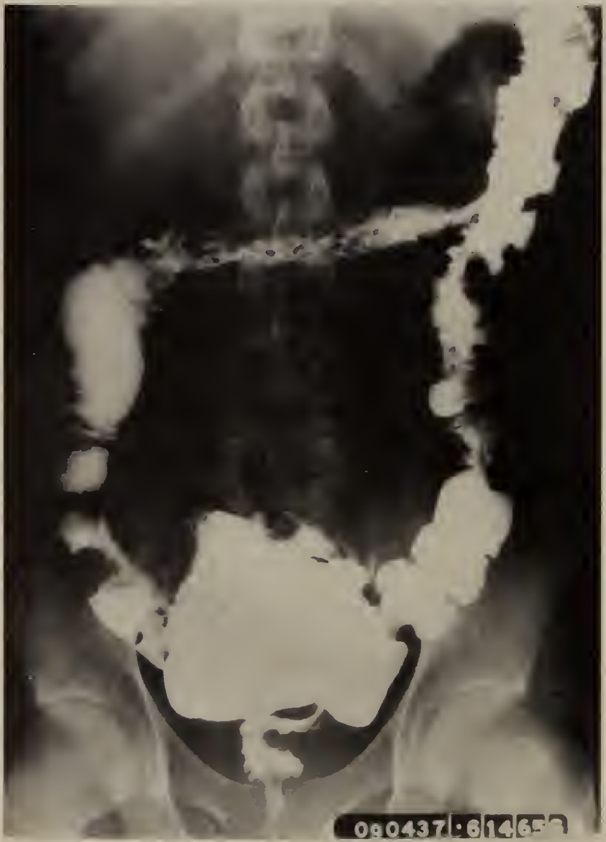

Figure 4.—Barium enema of a patient with Crohn's disease, illustrating skip areas in distal descending colon and near hepatic flexure with a "cobblestone" appearance of the transverse colon.

Complications, Prognosis and Management

The major complications of Crohn's disease have already been mentioned. Most are chronic and develop slowly. Those most commonly encountered are obstruction, rarely complete, fis-

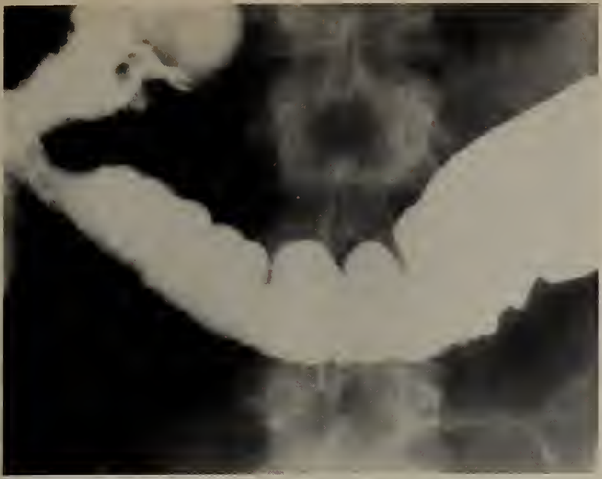

Figure 5.—Transverse colon of patient with Crohn's disease, showing asymmetrical involvement along inferior margin.

tulization, abscess formation, malnutrition, and anal ulceration. Hemorrhage and free perforation are uncommon. Toxic megacolon has been reported in a number of patients with granulomatous colitis[107,108] and is probably more common than previously believed. In most, the diagnosis of Crohn's disease instead of ulcerative colitis is only appreciated after colectomy. Since experience is limited its prognosis and optimal management remain undefined. Emergency colectomy is probably indicated in most, however, since a preoperative distinction from ulcerative colitis usually cannot be made.

The development of carcinoma in areas of bowel involved by Crohn's disease is also distinctly uncommon and is not generally considered in the overall management of the patient. Seventeen cases of adenocarcinoma of the small bowel in association with Crohn's disease have been reported.[109] In contrast to other adenocarcinomas of the small bowel they tend to be multicentric and to occur more frequently in the ileum and at a younger age. Thirty percent have developed in bypassed segments of bowel and most have presented as acute intestinal obstruction in a patient with a long history of Crohn's disease.

It is also not commonly appreciated that there is a relatively high incidence of gallstones in patients with long-standing Crohn's disease of the terminal ileum—reported at 30 percent in two different series.[110] This is not surprising considering the importance of the terminal ileum to bile salt metabolism and the relationship of alterations in the latter to gallstone formation. In patients with abnormalities or loss of the terminal ileum there is an increase in the ratio of glycine to taurine conjugated bile acids in the duodenal contents. In two patients this abnormality was present before any radiologic change in the terminal ileum was observed.[111]

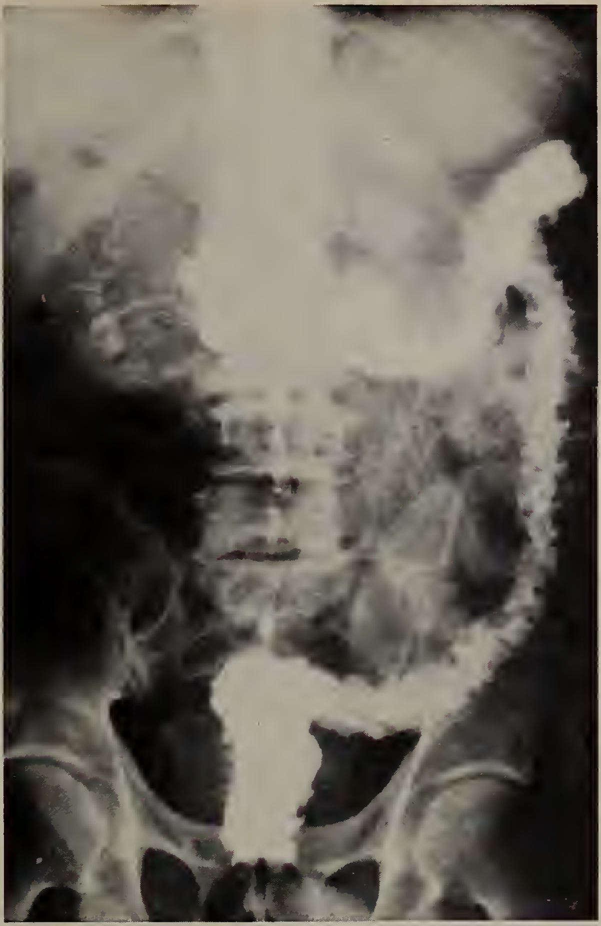

Figure 6.—Barium enema study of patient with ulcerative colitis, showing contiguous involvement of distal half of colon with characteristic mucosal ulcerations.

The prognosis of Crohn's disease has been difficult to define since it often depends on confirmation of the diagnosis by surgical means and on the length of observation. It has generally been considered to be a chronic disease of high morbidity and low mortality, with physicians often trying to recall when they had last witnessed an autopsy on a patient with the disorder. The overall mortality is probably in the range of 15 percent.[112] In a study by Prior et al of 295 patients followed for one to thirty-eight years, there were 53 deaths, which was more than twice the normal expectation for either sex.[113] There was also a tendency for mortality to be higher in those with onset before age 40 and if corticosteroids had been employed.

There is also a widely held view that Crohn's disease does not often spread to other parts of the bowel unless operation has been done. Brahme and Wenckert examined 36 patients over a period of time before operation and documented spread in 20.[114] Extension most often occurred contiguously in an aboral direction. In some cases lesions disappeared in one area and reappeared more distally. Extension was usually associated with an increase in symptoms but occasionally occurred in asymptomatic patients receiving steroids.

To a great extent the management of patients with Crohn's disease makes use of the same forms of therapy employed in the treatment of ulcerative colitis. Substantial differences exist, however, in the manner of application and in the results obtained.

The two most important factors influencing the outcome of treatment are the extent and location of disease rather than the severity of attacks. There is not the sense of urgency which attends the management of ulcerative colitis, since complications tend to be slow in developing and are less catastrophic. Again it should be emphasized that medical therapy is symptomatic. Measures to reduce the frequency of bowel movements may be helpful. In patients with areas of stenosis, however, such measures may only enhance signs of obstruction. Lomotil especially may cause increased abdominal pain and distension. The cautious use of belladonna is perhaps more helpful. Azulfidine has not proved as effective in Crohn's disease as in ulcerative colitis but does seem to have value. Except for the occasional patient with alactasia arbitrary dietary restrictions have no place in management. The diet should be as liberal as experience will allow and frequent small feedings are often more easily tolerated. Physical rest during exacerbations may also prove beneficial when coupled with the above measures. Crohn's disease in a way resembles rheumatoid arthritis in that response to treatment tends to be slow and gradual if it occurs at all. Again, it is extremely important that the patient understand his disease so that he becomes neither unduly discouraged nor falsely optimistic.

Corticosteroids and ACTH have also been employed and the immediate response in terms of clinical, biochemical and hematological parameters has been good in about 60 percent of patients. It is becoming increasingly clear, however, that continued use of steroids not only carries little if any benefit but in fact may be hazardous. Fielding and Cooke found that operation was twice as frequent in steroid-treated patients and mortality doubled.[115]

The surgical management is less satisfactory for Crohn's disease than for ulcerative colitis. This is due to the frequent necessity for resection of physiologically important amounts or areas of bowel and the relatively high recurrrence rate. As in ulcerative colitis, it is the patient not his bowel per se that is important. Roentgenographic abnormalities, the presence of fistulae or even an abdominal mass are not in themselves indications for operation. It is when the disease has begun to significantly interfere with the patient's overall health and well-being that surgical intervention may be required. Operative mortality is in the range of 3 to 5 percent,[116] with most deaths due to some form of sepsis or pulmonary embolism.

Resection is preferable to bypass, since it avoids leaving inflamed and often infected tissue and obviates potential problems with blind loops. Approximately 75 percent of patients with either small or large bowel disease will require some operation within five years of diagnosis.[86] The objective of the surgeon should be to remove all diseased tissue yet preserve as much normal bowel as possible.

Recurrence rates vary from 30 to 65 percent depending upon the distribution of disease at the time of operation. Recurrence is least frequent with disease limited to small bowel, especially terminal ileum, somewhat more frequent with colon involvement and most likely in the presence of ileocolitis.[117] Approximately 30 percent of patients will require more than one operation and the risk of recurrence rises somewhat with each successive operation. Krause et al[117] advocated radical resection, removing 10 cm of macroscopically normal bowel on either side of the diseased segment. With this approach they were able to reduce at least the early recurrence rate in one group of patients from 68 percent to 19 percent. They also felt that recurrences tended to be less severe.

It should be borne in mind that operation may still be worthwhile even if recurrent disease develops, since the symptoms of recurrent disease may often be less. Most recurrences are diagnosed within two years of operation. They occur on either side of the site of anastomosis, with a predilection for the proximal side.

Diverting procedures such as temporary ileostomy or colostomy and ileorectal anastosmosis were thought to offer an attractive alternative to resection, especially if the latter resulted in a permanent ileostomy. The combined experience of several studies, however, has been uniformly unfavorable.[118-120] A few successes can be expected with ileorectal anastomosis if the rectum is normal and all proximal disease is removed. This approach should be attempted before resort to permanent ileostomy. A possible exception is the severely depleted and malnourished patient in whom a temporary diversion may allow for resectional operation to be carried out under more optimal conditions. The experience of Glotzer et al[121] suggests that if all diseased tissue is removed and a permanent ileostomy performed the recurrence rate in the remaining small bowel is much less than with re-anastomosis. It is in fact rare for granulomatous colitis to exhibit progressive proximal spread after colectomy and ileostomy.

Anal and perianal complications seldom respond permanently or adequately to anything short of resectional operation.[122]

Ileostomy revision is required in nearly 25 percent of patients with Crohn's disease.[84] The nature of the ileal abnormality is debated and at present uncertain. In some it represents recurrent Crohn's disease while in others it is a more superficial inflammation possibly secondary to stomal obstruction.[123]

Although operation should perhaps be better later than early in Crohn's disease, the physician carrying out conservative management should not delay to the point of presenting the surgeon with an unacceptable operative risk.

Therapy with Immunosuppressants

Due to the frequently unsatisfactory results obtained with medical therapy in both ulcerative colitis and Crohn's disease, and because both have immunological overtones, it is only natural that treatment with drugs classified as immunosuppressants would be employed. Their use at present is entirely empirical and although short-term complications can largely be avoided by proper control of dosage, long-term hazards remain undefined. They have been used in ulcerative colitis during the past ten years and at least nine major studies have been reported.[124] Improvement has been observed in some patients but it is still not certain that their use is justified. No adequately controlled evaluation of their use has yet appeared. The preliminary results of a controlled therapeutic trial now in progress at Oxford have not been encouraging.[124] Use of immunosuppressant agents should be confined to such studies at large centers until their possible role has been defined. Reports concerning their use in Crohn's disease are appearing in increasing numbers.[125-128] Although some successes have been noted especially in the healing of fistulae, the reports are anecdotal; what is needed is well designed and adequately controlled studies. Use of immunosuppressants in patients with Crohn's disease who have significant morbidity and whose disease is too extensive for surgical treatment is probably justified, but apparently good results in the occasional patient should not be taken as an endorsement for general use.

Summary

It is obvious from the foregoing discussion that in many, probably most, instances, ulcerative colitis and Crohn's disease appear to be distinct and separable entities clinically, radiologically and histopathologically. It is also true that they share many familial, ethnic and immunological factors, and as many as 20 percent of cases of large bowel disease cannot be fitted into one of the two available types. The findings of Glotzer et al[121] are of particular interest in this regard. They placed patients into four histological groups on the basis of ulcer depth and the presence of sinuses or granulomas. At the same time they classified patients as either ulcerative or granulomatous colitis on clinical grounds. The presence of sinus tracts and granulomas correlated well with a clinical diagnosis of granulomatous colitis but when the two disorders were defined by the combined clinical and histological criteria there were no differences in mortality, age of onset, extra-intestinal manifestations or recurrence rates after colectomy and ileostomy.

In another study of patients with an initial histological diagnosis of granulomatous colitis who underwent a second resection, the second histological examination was frequently found to be more compatible with ulcerative colitis.[129]

Whether we are dealing with distinct entities having overlapping manifestations or a spectrum of a single disease remains unclear. In either case differences exist which have prognostic and therapeutic relevance.

An optimistic physician, a vigorous yet rational therapeutic approach, and a well-informed patient are the factors that combine to offer the best hope for successful management.

Trade and Generic Names of Drugs

Azulfidine®	salicylazosulfapyridine
Lomotil®	diphenoxylate hydrochloride with atropine sulfate
Metamucil®	psyllium hydrophilic muciloid

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Refer to: Clinical application of HBE (His bundle electrocardiography) in localization of atrioventricular defects—Medical Staff Conference, University of California, San Francisco. Calif Med 117:42-45, Jul 1972

MEDICAL STAFF CONFERENCE

Clinical Application of HBE (His Bundle Electrocardiography) in Localization Of Atrioventricular Defects

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* At Medical Grand Rounds today we are pleased to have Dr. Melvin Scheinman discuss the clinical application of the technique of His bundle electrocardiography.

DR. SCHEINMAN:† The ability to record electrical potentials from the region of the His bundle has introduced an exciting new chapter in clinical cardiology. The application of this technique has increased our understanding of cardiac arrhythmias and of the electrophysiology of the pre-excitation syndromes. However, the most important contribution of this technique is that it allows more precise localization of atrioventricular (A-V) conduction delays. Our purpose today is to discuss the technique, interpretation and clinical application of His bundle electrograms (HBE) in patients with A-V conduction delays.

Normally, the sinus node is the dominant cardiac pacemaker because its rate of spontaneous depolarization is more rapid than that of other intracardiac pacemaker cells.[1] The impulse from the sinus node is transmitted to both the atria and the atrioventricular node by means of specialized internodal tracts.[2] Depolarization of the A-V node is followed by sequential activation of the His bundle, the left and right bundle branches, the Purkinje's network and, finally, the ventricular myocardium. The His bundle is normally 2 to 3 mm in length, originates from the A-V node, penetrates the fibrous skeleton of the A-V valve rings and membranous ventricular septum, and finally gives rise to the right and left bundle branches.[3] The anatomical arrangement of parallel collagenous septa between His bundle fibers might conceivably result in longitudinal dissociation of the electrical wave front within the His bundle.[4]

Atrial and ventricular depolarizations are recorded as P and QRS waves on the surface electrocardiogram. Electrical depolarizations of other intracardiac-conducting tissues are not seen on routine electrocardiograms because the electrical activity is generated by relatively small structures buried deep within the heart. It is thus readily apparent that A-V conduction disturbances, manifested either by dropped ventricular beats or by prolongation of the P-R interval, may result from disease at the atrial, A-V nodal, or His-Purkinje level.[5] The application of newer techniques of measuring intracardiac potentials allows for more precise definition of the level of conduction delay.

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†Melvin M. Scheinman, M.D., Assistant Professor of Medicine.

Technique

His bundle recordings are obtained by a multipolar electrode catheter inserted percutaneously into either femoral vein and positioned across the septal leaflet of the tricuspid valve.[6] Right bundle branch potentials can sometimes be recorded as the catheter is advanced into the right ventricle and A-V node potentials, as the catheter is withdrawn from ventricle to atrium.[7] The His bundle potential appears as a sharp spike between atrial and ventricular waves. Atrial depolarization, or the "A" wave in the HBE, is assumed to represent low atrial activity so that the time interval between the "A" and the His spikes (A-H interval) represents, for the most part, the conduction time through the A-V node. The interval from the His spike to the onset of ventricular depolarization (taken from whichever lead shows earliest ventricular depolarization), or H-V time, represents conduction through the His-Purkinje system. If, in addition, a separate bipolar catheter is positioned at the junction between the superior vena cava and the right atrium (in the region of the SA node), then simultaneous electrical recordings from this catheter and the "A" wave in HBE allow measurement of interatrial conduction time.[8] Finally, conduction times from the His bundle to the right or left bundle branches (the latter obtained by catheterization of the left side of the heart) and from these latter structures to the ventricular myocardium can also be obtained with this technique.[9] Thus, clinical application of this technique adds another dimension in enabling the clinician to characterize atrioventricular and intraventricular conduction delays. In brief, prolongation of the A-H interval (normal, 70 to 120 msec) reflects A-V nodal disease or, more precisely, disease proximal to the His bundle recording site (Figure 1), whereas prolongation of the H-V reflects disease in the His-Purkinje system (normal, 35 to 55 msec) (Figure 2). Similarly, ventricular beats that are blocked below the His bundle show a His spike following each "A" wave (Figure 3), whereas beats blocked at the A-V node show absence of a His spike in the His bundle recording (Figure 3).

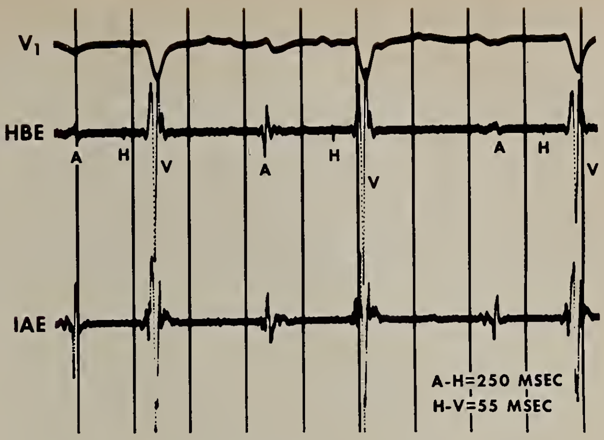

Figure 1.—Simultaneous surface (V_1 lead), His bundle (HBE) and interatrial (IAE) electrograms are recorded. The His potential (H) is seen as a sharp spike between low atrial electrical activity (A) and ventricular depolarization (V). Normal A-H interval is 70-120 msec while normal H-V is 35-55 msec. The prolongation of the A-H interval localizes the conduction delay proximal to the His bundle and, therefore, most likely at the level of the A-V node. (Paper speed 100 mm/sec; time lines 200 msec apart.)

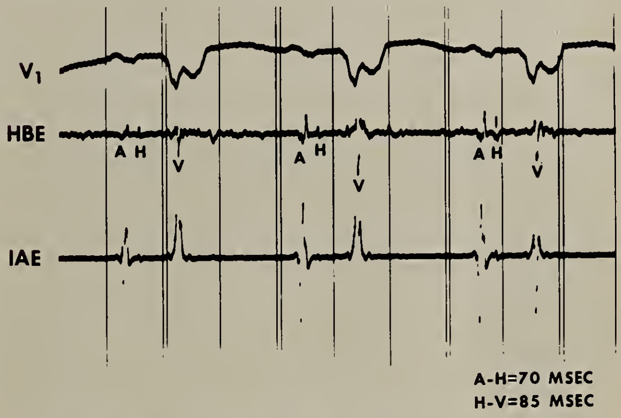

Figure 2.—Simultaneous V_1, His bundle and interatrial electrograms are recorded. The prolongation of the H-V interval localizes the disease to the His-Purkinje system. (Paper speed 100 mm/sec; time lines 200 msec apart.)

Common practice electrocardiography divides A-V conduction disturbances into three general groups:[10] First degree A-V block in which the P-R interval is prolonged; second degree A-V block which is subdivided into Mobitz I, or Wenckebach block (characterized by partial progressive prolongation of the P-R interval preceding a

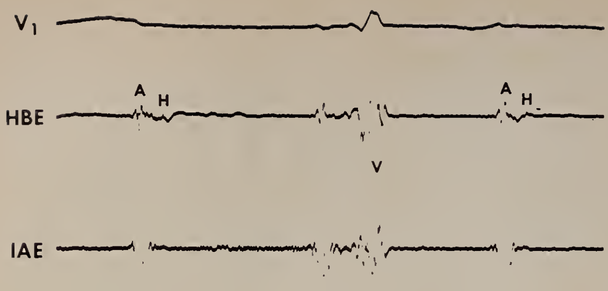

Figure 3.—Simultaneous recordings of V_1, His bundle (HBE) and interatrial electrograms. The surface electrogram shows complete heart block; note that each "A" wave is followed by a His deflection thus localizing the block to the His-Purkinje system. (Paper speed 100 mm/sec; time lines 200 msec apart.)

blocked QRS), and Mobitz II block in which the P-R interval remains stable until the blocked beat; and third degree A-V block, which occurs when no atrial impulse captures the ventricle. Furthermore, clinical anatomical studies suggest that Mobitz I block is generally functional and localized to the A-V node, whereas Mobitz II block is associated with structural infranodal disease.[11,12] His bundle and clinical electrocardiographical studies have revealed exceptions to this finding.[13,14] Perhaps a more meaningful clinical characterization of A-V block can be constructed on the basis of not only the type of block but also the presence or absence of QRS prolongation.[14] Preliminary postmortem anatomical studies of the conduction system in patients with infranodal disease determined by the His bundle recordings showed extensive, usually fibrocalcareous disease involving the infranodal conduction tissue.[15]

Detection of patients with severe disease involving the His bundle or the right and left bundle branches, or both, is of great importance since it is this group that is prone to the development of complete heart block with unreliable subsidiary pacemaker and resultant Stokes-Adams attacks. Varying electrocardiographical patterns of bilateral bundle branch block have been correlated with anatomical disease in this area.[16] For example, a retrospective study by Lasser and associates[17] showed that the most common electrocardiographical pattern antedating complete heart block is right bundle branch block and left axis deviation. Moreover, preliminary prospective studies showed that this electrocardiographical pattern of bilateral bundle branch block is accompanied by a high incidence of sudden death.[18] Unfortunately, the electrocardiographical pattern of bilateral bundle branch block is not uncommon, being found in some one percent of electrocardiograms processed through a hospital heart station.[17] Moreover, many people with this pattern remain asymptomatic for many years; and we therefore believe, on the basis of current information, that prophylactic permanent pacemaker insertion is not warranted for all patients with this electrocardiographical pattern.

His bundle studies may, however, be an important tool in helping clinicians detect those patients who will ultimately require permanent pacing. I would, therefore, like to summarize our experience with the use of HBE in symptomatic patients with the electrocardiographical pattern of bilateral bundle branch block. It should be emphasized that in our patient population dizziness, syncope, and seizures are most often a result of acute or chronic alcoholism or cerebrovascular disease, or both; therefore, the occurrence of these major symptoms and an electrocardiographical pattern of bilateral bundle branch block do not invariably mean that the patient requires a permanent intracardiac pacemaker.

The data for nine patients with major symptoms and electrocardiographical findings of bilateral bundle branch block studied over the past eight months are summarized in Table 1. In Group I, symptoms were attributed to noncardiac causes, and after a mean follow-up time of 5.4 months none of the patients had documented Stokes-Adams attacks. In Group II, all patients had documented periods of complete A-V block or Stokes-Adams seizures, or both, and therefore underwent insertion of a permanent transvenous pacemaker. It is of interest that the patients in Group II had decided prolongation of the H-V interval, whereas those in Group I had minimal prolongation of this interval. It is obvious that sweeping conclusions are unwarranted on the basis of our present meager experience, but our working hypothesis is that patients with bilateral bundle branch block and marked prolongation of the H-V interval have an increased risk for the development of third degree A-V block and Stokes-Adams attacks.

TABLE 1.—*His Bundle Recordings in Symptomatic Patients with Bilateral Bundle Branch Block*

	Group I			*Group II*	
Patient	A-H (*msec*)	H-V (*msec*)	*Patient*	A-H (*msec*)	H-V (*msec*)
1	106	66	4	100	120
2	75	60	5	100	90
3	84	70	6	(AF)*	70
			7	120	105
			8	190	85
			9	60	140

Group I: Patients with major symptoms not attributable to Stokes-Adams attacks.

Group II: Patients with major symptoms attributed to Stokes-Adams seizures (all requiring permanent pacemaker therapy).

*Atrial fibrillation.

The technique of recording His bundle potentials is simple and does not expose the patient to undue risk. To date we have performed over 50 His bundle electrograms without serious complications in patients with complex arrhythmias or A-V conduction disturbances, or both. We think that this technique gives valuable insight into the physiology of cardiac rhythm disturbances and yields information that may be of great importance in direct patient care.

Summary

His bundle potentials are recorded from a multipolar catheter positioned across the tricuspid valve. This technique allows for more precise localization of A-V conduction disturbances. The technique is simple and safe and may be performed readily in any cardiopulmonary laboratory. The information derived gives the clinician greater insight into mechanisms of cardiac rhythm and conduction disturbance that may aid in direct patient care.

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CONGENITAL ESOTROPIA—REFER EARLY

I think many physicians become concerned about when to refer a child for evaluation of a congenital esotropia condition. I would say by four or five months of age, if a child's eyes are obviously crossed, there's no doubt that the child will need some surgery and that the earlier this is done the better. In fact, it's routine now for many ophthalmologists to operate on children with congenital esotropia at about six months of age.

I think it's important to examine these children quite early. We have seen a couple presenting with crossed eyes who really harbored a retinoblastoma in one eye or the other. We've also seen children with congenital toxoplasmosis lesions involving the macula present in this way.

—EARL L. STERN, M.D., San Francisco

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Important Advances in Clinical Medicine

Epitomes of Progress -- Psychiatry

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Psychiatry. Each item in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Psychiatry which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panels to the Section on Psychiatry of the California Medical Association and the summaries were prepared under their direction.

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Current Patterns of Drug Misuse

DRUG MISUSE may be currently divided into seven categories. By far the most common drug of abuse remains alcohol; 5.5 percent of all drinkers are estimated to suffer eventually some syndrome of alcoholism. Barbiturates constitute the next most serious drug abuse pattern; a death rate of 25 per 100,000 population may be anticipated in urban areas, particularly on the east and west coasts. There are an estimated 50,000 active heroin addicts in California, an increasing number of whom are from the middle and upper classes. Amphetamines remain a drug abuse problem in the form of excessive medical prescription for antidepressant and weight control problems; use from illicit sources also continues to be a problem. Intravenous injection of amphetamine appears to be significantly diminishing, subsequent to the reports of the polyarteritis nodosa syndrome. The inhalation of solvents continues to be a problem among disadvantaged and minority groups, and has recently appeared among some Indian groups. The use of marijuana and other hallucinogens, continues to be the most major drug abuse problem, primarily in terms of the immense social cost related to criminalization. Cases of acute psychotic reaction to marijuana, and other hallucinogens, are now rarely seen in emergency facilities, despite the fact that the use of marijuana is increasing at an estimated rate of 20 to 30 percent per year. The estimated rate of arrest is 31 per 100 for the sale of illicit substances and 3.1 per 100 for the personal use of marijuana. Despite these significant risks, legal deterrents have had no appreciable effect on the increasing use of these substances.

JOEL SIMON HOCHMAN, M.D.

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Mental Health of American Indians

THREE MAJOR MENTAL HEALTH problem areas are prominent among North American Indian groups: Childhood disability, particularly in reference to the educational system; alcoholism; and suicide.

The education of Indian children is characterized by scholastic failure and under-achievement. This is not due to innate lack of ability, but is the result of an educational system which instills a negative identity. The resulting low self-esteem guarantees academic failure. Other indicators of psychiatric disability such as anxiety, depression, withdrawal and antisocial behavior are present. This is nowhere more apparent than in the boarding schools. Here the child is placed in an unfamiliar environment, far from home, among alien adults who have established an environment which in some instances makes most juvenile detention facilities seem like Summerhill. This childhood educational experience poorly equips the Indian adolescent for life on or off the reservation and sets up the self-fulfilling prophecy of failure, drunkenness and self destruction. Indian parents have had little input into the educational system until recently. The success of some Indian run schools ought to be a model, but unfortunately the participation of Indians in running their own schools either on reservations or at boarding schools, is a rare event.

Alcoholism is epidemic on many reservations and among Indians who have migrated to urban settings. Feelings of powerlessness, wishes to relieve unpleasant affective states, breakdown of traditional behavioral controls and facilitation of social participation, have all been cited as causes of Indian alcoholism. Basic, of course, is a fragmented sense of identity and low self-esteem. There is no basis for the belief that Indians have a decreased tolerance for alcohol. It is, rather, that Indians have developed different patterns of alcohol use than is seen in western society. Of further interest is the fact that a disproportionately high number of Indians are found in state and county prisons, a factor primarily due to increased rates of arrest and conviction for alcohol related offenses.

The problem of suicide among some American Indian groups has gained national attention. On some reservations, rates as high as 100:100,000 have been recorded. This is ten times the national average. A recent review article by Resnick and Dizmang detailed this situation. The causes of the increased rate of suicide are similar to those cited for alcoholism, particularly the incorporation of a negative self image and diminished self esteem. Most Indian suicides are of young, single men. One study indicates that a disproportionately high percentage of suicidal young men come from backgrounds characterized by the presence of diverse caretakers during childhood. More studies are needed to clarify the cultural and interpersonal factors related to Indian suicide.

It is important to consider the Indian in terms of his own identification. The traditional patterns that change from tribe to tribe are more varied than most westerners realize. Among Indians who have migrated to urban settings, tribal ties are loosened. Recently, a pan-Indian movement was developed that replaces and coalesces various tribal themes. A dominant concern among both urban and tribal Indians is the importance of Indian direction of mental health programs.

JAMES T. BARTER, M.D.

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Psychoanalysts View Aggression

The 27th Congress of the International Psychoanalytical Association addressed itself to the subject of aggression. Psychological evidence was offered viewing aggression as an instinctual drive as yet unrelated to any physiological phenomena other than brain functioning. The discharge of aggression is associated with pleasure and the lack of discharge with unpleasure. The aim of aggression is not necessarily the destruction of the object, but varies with the mental development and experience of the aggressor. It is not known whether aggression and sexuality are separate at birth and gradually fuse during development, or whether the two differentiate from a common matrix.

A plea was made, at the meeting, for interdisciplinary research to bring the problem of aggression closer to solution. The sociologist can assist in the study of collective aggression in large groups, and also assist psychoanalysts in making a significant contribution to the examination of a society at war, in a state of rebellion or other violent disturbance. The vicissitudes of individual life, as seen in early object relations, and the vicissitudes of social life based on the objective conditions of a community must be explored by combining psychoanalytical and psychosocial research. From this cooperation with other humanistic sciences, it is hoped that the analytic researcher will fashion a more precise evaluation and diagnosis relative to the origins and fate of aggression.

S. Lawrence Pomer, M.D.

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Wrist Slashers

A study of police reports revealed that people who cut their wrists are younger, more often single and more often male than those who attempt suicide by other means. Wrist slashers are no more likely to repeat attempts at suicide than others. The commonly held belief that women far outnumber men as wrist cutters was not verified possibly because women attempters are more likely than men to seek treatment in private facilities.

In the emergency room, efforts should be made to establish the complex significance of the slash. The patient's ego controls should be assessed and hospitalization of the psychotic slasher, including stringent suicide precautions, is necessary. Psychotic guilt is a serious sign of suicidal intent, and such patients are to be expected to try again. Optimal treatment of slashers includes psychotherapy tailored to specific situations and personality structures.

S. Lawrence Pomer, M.D.

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Black Physicians and Black Clients—Is It "A Family Affair"?

The black physician, as a result of his traditional medical training, even if in a black college, may unwittingly adopt stereotyped values toward other helping disciplines, such as psychiatry and psychology, because of the necessity in his training program to meet white approval in order to be legitimized.

Admittedly, the black physician, in his work with the "colonized" black patient, is usually innovative when he is effective. This is not to imply that the value of his traditionally approved training should necessarily be minimized, for when the black physician "respects himself," he will have no difficulty working on either side of Wilshire Boulevard applying "different strokes for different folks."

In psychiatric circles, in particular, a considerable amount of literature has accumulated that discusses issues arising between black therapists and white clients, and between white therapists and black clients.

Unique problems can also arise when the therapist and client are both black. Themes that frequently present as countertransference issues include denial of identification, overidentification, and class differences and similarities between therapist and client. External and internal obstacles to be mastered by the black psychiatrist at leadership helms, if he is to be effective in his relationship with black clients, include professional identity hurdles, personal anxieties and fears, ethnic identity issues and leadership problems.

These hurdles can be overcome when the black physician can resist the seductive notion that his "black skin" adequately substitutes for objectivity and scholarly endeavor.

These issues have relevance, not only for the black physician and black client, but also for white medical professionals who will increasingly be mentors to black trainees in otherwise predominantly white medical centers.

ELVIN MACKEY, JR., M.D.

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Psychiatric Emergency Services

COMMUNITY NEED for 24-hour, 365-day, comprehensive psychiatric emergency services (PES) is now commonly recognized. Basic program elements include: (a) telephone interviewing; (b) walk-in evaluation; (c) continuous observation and treatment capability for up to 12 to 24 hours; (d) referral and referral-success check system; (e) capability for serving involuntary as well as voluntary patients; and (f) linkage to a medical-surgical emergency service, and to psychiatric hospital, outpatient crisis, drug and alcohol abuse intervention units. Other desirable features are: (a) a physically separate area to house the PES; (b) follow-up visit capability for up to one week; and (c) mobile unit for community service.

Common intervention modalities include: (a) the preliminary evaluation itself, in which clarification, catharsis and reassurance are frequently therapeutic; (b) counseling with patient and relatives; (c) medications; (d) on-unit patient group activities; (e) environmental manipulation; and (f) PES-catalyzed natural improvement. These techniques quickly reduce emotional and behavioral disturbance and often prevent psychiatric hospitalization, especially for many transiently anxious, angry, intoxicated, depressed, and initially suicidal patients.

A PES should always have a physician on duty (psychiatrist or other physician with telephone back-up by a psychiatrist) because of the frequent acute psychotic and delirious states requiring differential diagnosis and rapid drug therapy. Nursing personnel require special in-service training in emergency intervention. Well trained and supervised non-professionals (volunteers or indigenous paid mental health workers) participate ably in several aspects of intervention. Child PES visits are uncommon, but a good service should have child mental health consultation available by telephone.

The major problem of the PES is the high cost of its safe and successful operation. However, a well run, well-linked PES reduces yet more costly service, therefore justifying this expense.

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The Lateral Specialization of the Human Brain for Cognition; EEG And Lateral Eye-Movement Studies

WE ARE STUDYING the lateral specialization for cognitive function. In one study, we recorded the EEG from the temporal and parietal areas of both hemispheres while subjects were performing verbal and spatial tasks. We expected verbal tasks to engage the left hemisphere predominantly, and spatial tasks to engage the right. During the verbal tasks the amount of alpha rhythm in the right hemisphere increased relative to the left, and during spatial tasks the alpha in the left hemisphere increased relative to the right. In general, the ratio of right hemisphere power to left hemisphere power was greater on left hemisphere tasks than in right. This ratio can be used as an index of the relative involvement of each hemisphere in a given situation.

We then used this index RH:LH power as a cue in a biofeedback study. Our results indicate that subjects can voluntarily regulate this index, and thus the amount of each hemisphere's involvement in a situation.

David Galin, m.d.
Robert Ornstein, ph.d.

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Kocel K, Galin D, Ornstein R, et al: Lateral eye movement and cognitive mode. Psychonomic Science, in press

Newer Approaches to Drug Abuse

The major developments in the last year in treating drug abuse have centered around the increasing use of methadone therapy for heroin addiction. The increasing sophistication in the use of this controlled addiction has resulted in more careful selection of patients, control of the substance and the necessity of adjunctive group and vocational techniques for optimum effectiveness. Although other inpatient and day care group techniques are successful with selected patients, the use of methadone maintenance appears to diminish the complicating social and criminal problems associated with this addiction. In other areas of drug abuse there have been no major new developments. Attention has been mainly on the early detection, prevention of criminalization and expansion of the group and family techniques at all levels of the community.

Robert J. Sokol, m.d.

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Behavior Therapy

Behavior therapy, behavior modification, behavioral engineering, and contingency management are terms used interchangeably in the psychological literature to refer to the application of principles of social learning theory to modify human behavior labeled as deviant. Behavior therapy is a new therapeutic technique effective in modifying behavior which is initiated, inhibited or maintained by the environment, and it is inexpensive.

Behavior therapy was suggested first in the 1950s simultaneously by work with schizophrenics and neurotics. The field has experienced an explosion of application in the past decade with half a dozen journals now established and literally thousands of research articles available. The application of behavior therapy implies a radical reconceptualization of psychopathology from a disease model to the understanding of deviant behavior as learned, and therefore subject to modification by new learning. The therapeutic strategy is closely tied to its research base by demanding careful description of target behaviors (for example, symptoms) in the baseline period, specification of the therapeutic intervention, observation of behavior change, and long term follow-up.

Behavior therapy is effective in increasing infrequently occurring, but desirable behavior, when immediate positive reinforcement is contingent to the patient's behavior; and in decreasing frequently occurring destructive or deviant behavior by pairing its occurrence with either noxious stimuli or by letting it go unreinforced. In addition to its application to individual patients, attention to the interactional and interpersonal context of behavior has led to such innovations as the "token economy" model employed to modify patterns on in-patient psychiatric wards, residential treatment facilities for juvenile delinquents, and with mental retardates. Behavior therapy is frequently the treatment of choice in the management of the disruptive child in the classroom, or in the family. It is used extensively in special education classes.

The technique is inexpensive because the principles of social learning theory can be taught to the full range of mental health professionals and paraprofessionals. More importantly, simple programmed texts have been developed for those individuals who have maximum influence over the social and environmental contingencies of children, namely, their parents, teachers and peers.

Margaret S. Steward, ph.d.

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Genetics of Human Violence

Aggression and violence have become center issues in our society. Suicide, homicide, assaults, racial conflicts, war, atomic destruction and genocide are but a few of the topics that now demand serious professional attention. Certain statistics help focus the problem: In 1967, someone was shot to death in the U.S.A. every 25 minutes and guns were involved in some way in the deaths of 21,000 civilians. Two drugs associated with violent acts are alcohol and the amphetamines. In a review of television programming six weeks after Robert Kennedy was assassinated, the following was observed: In 85½ hours of programming in prime evening hours and on Saturday morning, 84 killings were observed. The most violent hours of television were between 7:30 and 9 p.m. During that time, 26.7 million children between ages 2 and 17 were watching television. Certain researchers now feel they have demonstrated that television definitely influences the behavior of children.

Much research is currently being conducted into these complex areas. One of the most interesting findings is that man and the European Brown rat are the only known species that engage in species-destructive behavior. Konrad Lorenz has developed a theory which may explain this peculiar and species-endangering activity. In a cross cultural study of homicide, the availability of firearms is directly correlated with the incidence of homicidal deaths.

Many of these findings are of specific use to physicians, psychiatrists, police, educators and penologists.

Thaddeus Kostrubala, m.d.

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Short Versus Long Hospital Treatment of Schizophrenia

Despite the fact that there have been no controlled studies of the relative effectiveness of short-term and long-term hospital treatment of schizophrenia, community resources have primarily been allocated to short-term treatment. We have recently set up the first controlled study to measure the relative effectiveness of these two treatment strategies by randomly assigning each of 130 patients into either short treatment or long treatment and using a fixed phenothiazine dosage regimen. Short treatment is defined as 21 to 28 days, long treatment as 90 to 210 days.

Short-term strategy focuses around crisis intervention and immediate reestablishment of "community support systems." Long-term intervention involves phenothiazine control, greater flexibility in terms of diagnosis and management, psychotherapeutic exploration of precipitants that caused hospitalization, rehabilitation and extensive discharge planning. Both in-hospital and post-hospital treatment are evaluated by blind raters.

The follow-up period is limited to two years, because it is felt that "washing-out" of independent variable occurs at that time. It is hoped that predictor variables for schizophrenic patients can be identified so that the choice of hospital treatment will be a more rational decision.

Ira D. Glick, M.D.
William A. Hargreaves, PH.D.

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Encounter Groups

Encounter groups may include labels such as "training groups" and "sensitivity groups." The background of the leader may vary from extensive training to nothing but previous group participation. Generally participants in these groups consider themselves normal, and hope for a "growth experience." The group methods used are potentially very powerful, in both beneficial and destructive ways.

Yalom and his co-workers made extensive studies of a group of university students assigned to encounter groups with leaders of differing backgrounds and styles.

"Casualties," defined as enduring significant negative outcomes which were caused by participation in the group, occurred in 16 subjects, a figure approaching 10 percent of the 170 who completed the course. A casualty was most likely to occur in persons of low self-esteem and unrealistically high expectations from the group experience. The highest risk leadership style was characterized by high stimulus input, charisma, intrusiveness, and focus on individual rather than group or interpersonal dynamics.

These group experiences may be gratifying, stimulating and even insight producing, but the potential for psychological damage must be carefully evaluated in each situation.

John S. Peck, M.D.

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Ultradian Rhythms and Behavior

Sleep, as electrophysiologically measured, shows a striking temporal organization. There is an intrasleep cycle characterized by rhythmic alternation between rapid eye movement sleep and nonrapid eye movement sleep, with the length of the total cycle on the order of 100 minutes. Such fast frequency biological rhythms are designated "ultradian," in contrast to slower rhythms on the order of 24 hours which are termed "circadian."

Recent evidence suggests that an ultradian rhythm is also present during waking. Such rhythms have been detected in waking oral activity, performance on a signal detection task, and a number of psychological and physiological variables in subjects under sensory deprivation conditions. It may be that the prominent intrasleep cycle is only a reflection of a more general ultradian rhythm (the "basic rest-activity cycle") which continues throughout the 24 hours and which is of broad behavioral significance. Investigations into the temporal organization of behavior are of increasing interest, but the clinical relevance remains as yet unclear.

Gordon G. Globus, M.D.

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Current Approaches to the Study of Suicide Prevention

Present emphasis in studies of suicide prevention is on the improvement of predictive scales, the development of more effective intervention techniques and evaluation of the impact of suicide prevention programs.

Scales which quantify suicide risk are evolving in the direction of sets of variables applicable to a basic subtype. For example, Lettieri has developed a ten-item scale for women over 40 and an eight-item scale for women under 40, with only one item common to both scales. Chances of one to two-year survival as regards suicide are determined, assuming the person is a caller to a suicide prevention center. Scales for various subgroups derived from different populations are being developed by other investigators.

New intervention techniques involve radio-dispatched crisis teams, emphasis on face-to-face counseling as an extension of traditional 24-hour telephone referral services, and integration of suicide prevention into the broader field of crisis intervention.

A set of curricula for training in suicidology, for various professional and non-professional groups, has been developed by the NIMH Center for Studies in Suicide Prevention.

Current efforts to evaluate the effectiveness of suicide prevention programs are aimed primarily at the problem of nomenclature, which has made the observed suicide rate such an inadequate guideline.

JEROME A. MOTTO, M.D.

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His Bundle Electrocardiography

THE INTRODUCTION OF HIS BUNDLE electrocardiography has resulted in major advances in clinical cardiology. It has enhanced our knowledge of the mechanisms of the pre-excitation syndromes and has clarified the reentry mechanism of the supraventricular tachycardias. It is the definite method of differentiation between aberrant ventricular conduction and ventricular ectopy. On occasion electrocardiograms which are consistent with second degree A-V block are shown to be instances of concealed ectopic beats, an obviously more benign disorder. The most important contribution has been the identification of the site of A-V block. The P-R interval which represents the period of time from the onset of atrial depolarization to the onset of ventricular depolarization can now be divided into two segments, the A-H interval which is largely a measure of the A-V conduction time and the H-V interval which measures conduction through the His-bundle branch-Purkinje system. It is gratifying that His bundle recordings have confirmed the generality used in clinical electrocardiography, namely that A-V block with widened QRS intervals indicates block distal to the bundle of His and that such blocks have a more serious prognosis. However, this generality is by no means absolute and His bundle recordings permit exact identification.

His bundle recordings have increased our knowledge of the site of block resulting from commonly used cardiac drugs. Digitalis produces conduction delay proximal to the His bundle (hence in the A-V node) whereas quinidine and procaine amide produce distal block. The distinction between Mobitz I and Mobitz II types of second degree A-V block is now accurately made by His bundle recordings. The absence of a His spike following the nonconducted P wave indicates a proximal block in the A-V node (Type I). The presence of a His spike following a nonconducted P wave indicates a block distal to the His bundle (Type II). In third degree heart block the presence of His spikes preceding the QRS indicates a secondary pacemaker in or above the His bundle, whereas absence of His spikes localizes the pacemaker in the distal I-V conduction system.

A major problem in clinical medicine is the treatment of asymptomatic persons whose electrocardiograms indicate bifascicular or incomplete trifascicular block (bilateral bundle branch block). These include right bundle branch block with left anterior fascicular block, right bundle branch block with left posterior fascicular block, right or left bundle branch block with prolonged P-R interval and right bundle branch block with left anterior or posterior fascicular block and prolonged P-R interval. Right bundle branch block with left anterior fascicular block is the most commonly recognized and is known to be associated with a higher incidence of subsequent complete heart block and death. Is this an indication for routine pacemaker implantation in such asymptomatic persons? Since many such patients remain asymptomatic for many years, the current opinion is not to advise routine pacing. However, what about patients with other types of bifascicular or incomplete trifascicular block who are asymptomatic? No definite information is available at this time to adequately answer the question of pacemaker therapy in these patients. Long term studies with the aid of His bundle recordings are needed to resolve this problem.

In this issue of CALIFORNIA MEDICINE, Dr. Melvin Scheinman has succinctly reviewed the subject of His bundle recordings and has presented data on a small number of patients with bilateral bundle branch block. Although the number of cases is small, the evidence that definite prolongation of the H-V interval is associated with symptoms or electrocardiographic documentation of complete heart block necessitating permanent pacing is significant. Dr. Scheinman is continuing his investigations and it is hoped that such studies will yield information which will permit the physicians to identify the patients who are at highest risk of syncope or sudden death and who therefore require pacemaker implantation.

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Medical Electronics and Patient Safety

PHYSICIANS, HOSPITAL ADMINISTRATORS and nurses express concern over the rapidly growing number of electronic instruments which are used in health care facilities. These instruments have become increasingly complex and sophisticated. In most community health facilities there is duplication of machinery, resulting in great expense. This duplication stems from inter-hospital rivalry, the desire of each facility to meet the demands of an ill-informed public, and the demands of one or two specialists who believe that they can make significant use of these instruments.

Many serious situations have been created by: lack of pertinent information on the part of the purchasing agent; failure of responsible personnel to maintain an accurate inventory; lack of trained technicians to prepare instruments and keep them in satisfactory working condition for emergency use; and treatment personnel insufficiently knowledgeable as to either operation of the instrument or patient safety.

Because of these problems, the Association for the Advancement of Medical Instrumentation has been formed. This organization is functioning as a sounding board, a discussion group, and an advisory council for the purpose of education and consultation.

At the American Heart Association meeting in Anaheim in October, 1971, a speaker said that in 1970 there had been approximately 1200 electrocutions in the hospitals of the United States. This statement was questioned because if such an assertion were proven to be fact, then one in four of the 7,000 hospitals in this country would have experienced such a death. In the 170 hospitals in Area V of the California Regional Medical Programs, electric shocks have been experienced by patients or personnel or both, but there have been no known deaths, or serious morbidity. When the origin of the statement of 1200 deaths was traced, it was found to have come from a Swiss resident physician who, having intimate knowledge of such a death, then made a random estimate of 1200 electrocution deaths per year. In the absence of any statistical documentation, this statement should not be repeated.

The Administration in Washington has caused to be submitted to the Congress a Devices Bill. In December, 1971, Senator Javits (New York) introduced S-3028 and Representative Staggers (West Virginia) introduced H.R.12316 as identical bills. The Senate bill will go through the Health Committee, the House bill through the Interstate and Foreign Commerce Committee, and both bills are expected to be processed this year. If passed, the bills will authorize the Secretary of Health, Education, and Welfare to establish safety standards for devices and will require devices used in life-threatening situations to undergo scientific review by the Department for Safety and Efficacy before their introduction into commerce. The bills also provide the methods for review by an advisory committee of experts and for amendment or revocation of standards.

The bill incorporates extensive directives as to manufacturing standards, their review, prohibition, notification of defects, maintenance of records, registration and inventory. If the Devices Bill passes, it will probably open the way for regulation of all diagnostic kits.

The opponents—who include many physicians, manufacturers and pharmaceutical companies—fear that such legislation could impede innovative and individual initiatives.

Ever since the Bell Laboratory engineers came up with the transistor in the late 1940's, the medical profession has been placed in the position of trying to catch up with the many instruments which are appearing in our clinical laboratories and in the critical care areas of our hospitals. The result is that instrument sophistication presents a very real problem.

The quantity and quality of medical instrumentation has increased to that point where a recent Electronic Buyer's Guide listed 370 domestic companies and many foreign companies which are in the marketplace. Many of these companies list 150 major products or systems with complete specifications in their respective product lines. Thus, the 370 domestic companies, each with 150 items, provide the purchasing agent about 55,000 choices.

With these facts before us, how can we purchase the correct equipment and maintain our old instruments while at the same time insuring high standards of patient safety throughout a health care facility?

Medical specialization is growing rapidly, and with it there has been a corresponding increase in the number and type of paramedical specialists. More education and training for the increased number of people have cost the health care facilities sizable sums of money. Some hospitals have large pools of trained personnel from which to draw; others do not, and the result is that high-priced talent is wasting time in travel between work areas. For example, an electroencephalograph technician or a laboratory technologist may travel between four or five different hospitals or laboratories. The system of utilizing roving personnel has proved to be more or less of a detriment to the efficient operation and maintenance of equipment. These people have little time and give very little thought to the major responsibility of accuracy and patient safety. The factors of patient safety, electronic maintenance and operation are tightly secure in some areas of a hospital, such as an intensive care or coronary care unit; but this is not always true throughout the entire hospital.

Spiraling demands have brought about the desire to invest in programs of expansion, with multiplication of equipment, facilities and personnel. Federal assistance is often not readily available and therefore hospital administrators have become keenly interested in the cost factors of such programs.

A universal patient safety program—including reporting of equipment status, rates of use and operating costs for all instrumentation, as well as in-service training program costs in hospitals—is required. A recent inventory at one of our Los Angeles hospitals showed that of 58 instruments from 34 different companies, 15 were in need of immediate repair, and three had to be withdrawn from service. Many hospitals do not keep inventory records. They lack cost of operation data and they have no regular inspection or repair records except those made by the on-duty nurse. An equipment control system is imperative, not only to insure cost consciousness but also patient and personnel safety.

Patients are aware of new developments and they are demanding more and more of each health care facility. Community awareness has created a demand which will not settle for anything less than excellence from physicians and hospital personnel, and excellence in the quality of instrumentation. If we provide the best by our own initiative, perhaps government regulation, with which medical instrumentation is about to be confronted, will not be necessary. It is essential, however, that we exercise proper purchasing and inventory control and preventive maintenance.

Today, there is interaction between physicians, bioengineers, administrators and educators, so that patient, operator and machine constitute one system dedicated to the delivery of total health care. A new magazine, titled *Health Devices*, is an excellent guide for medical consumers. It is published by the Emergency Care Research Institute, a non-profit agency based in Philadelphia.

Medical instrumentation is a part of health care. We need to devote time and attention to this facet of care in order to insure availability, accessibility and safety without excessive dollar costs.

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Planning Health Care Services For a Free Society

THESE ARE TIMES WHEN we have only to look around us to see great interest and much governmental support for planning in the field of health care. So far all of this planning has accomplished far less than had been hoped or expected. It has not been clear exactly why this has been so, and perhaps some examination of planning health care services for a free society is in order.

There appear to be two extremes of attitude toward planning in health care. On the one hand there are those who are convinced that what they call the "non-system" of health care is so chaotic that it must be organized and regularized and that virtually any plan or system which could be put into effect would be a welcome improvement. On the other there are those who believe that any sort of planning will only serve to fetter the "system" and make it less responsive to individual needs or changing situations. For many reasons it seems unlikely that either a fettered system or free Brownian movement is likely to provide an acceptable answer to improving the delivery of medical and health care services in a free society.

A free society is something that has not always been thought about very much in discussions of planning for health care. Yet the American people are committed to the idea of a free society. It should be recognized that a planned society or a planned health care delivery system is really incompatible with the idea of a free society. It implies a curtailment of personal freedom and the probability of being forced into a system with a bureaucracy which in all likelihood will become progressively less responsive to changing needs and increasingly difficult for a free society to influence or direct. While it is clear enough that more organization and system is needed in health care, it is not yet so clear how this can be accomplished without destroying the very thing which makes a free society free. But this requirement of freedom is essential for the satisfaction of all concerned, and must be taken into account in any planning for health care which is to be acceptable in this country.

Planning is generally directed to the present, or the future, or sometimes to both. The subject matter in health care is complex and always changing. By the time the planners have agreed upon their assumptions (which are often more theoretical than realistic), gathered their data (which is usually difficult and time-consuming), developed their plan for the present (which is based on theory or untested belief) and before it can possibly be implemented, the situation is usually changed and may actually be quite different. Planning for the future is even more difficult and uncertain since in the health field the future has proved to be quite unpredictable.

Most of the planning we see now going on about us also seems to ignore certain human factors. For example, no one likes to be told by someone else what he will have to do, especially in a free society, yet the element of compulsion underlies much of the thinking in health care planning. One suspects that some planners may actually get their jollies out of creating something which will become a projection of themselves and impose their will upon others. But human nature is such that unless those who are to be involved in carrying out the plan have a hand in developing it, they are apt to distrust it, and also to distrust those who would try to impose it upon them. In short, they will not be satisfied with it, and experience shows they will do little to try to make it work. Rather the opposite, they will often try to destroy such a plan by conscious or unconscious sabotage, open or concealed hostility, non-participation or whatever. For these reasons, unwanted and distrusted plans often have to be implemented through the force of law if they are to be implemented at all. We see this beginning to occur with increasing frequency, but it hardly seems to be an ideal or sophisticated solution for a free society such as ours. Also it should be noted that even unwanted laws do not often work well.

What then can be the solution for planning health care services for a free society? It is suggested that only if planning can be a voluntary action on the part of the free society itself, those who are to carry out the plan, will the planning and plans be truly acceptable and truly workable without coercion. This suggests that in planning for health care services, providers (including physicians), consumers (including patients), payors (including health insurance agencies) and the public (including government at the appropriate level) must all be realistically involved in a truly cooperative effort. No one of these should dominate the planning process. It follows that the planning and plans for services must meet local needs and be locally controlled, not controlled by outsiders, if they are to work. The planning process and the plans themselves must be flexible and responsive to changing local needs and changing local circumstances. They must be living instruments and not inflexible structures or rigid systems, which either literally or figuratively can only be changed "by act of Congress."

We know of only one experiment with this approach to planning health care services in one community in California. There should be more. We believe it could be made to work.

—MSMW

Society Needs Its Physicians And Vice Versa

The need of any human society for its physicians antedates recorded history. This is a need which will not go away. But neither is it a foregone conclusion that it will always be physicians, as we know them, who will fill this need. If today's physicians abrogate or fail to fulfill their responsibilities as physicians to society, there is no question that society will simply designate another profession or elite group to act in the capacity of physician, with results which might be better, but would probably be worse for all concerned. Were this to occur, the medical profession as we now know it would be recognized merely as technical specialists, to be employed by society to perform certain specialized services under conditions which would be determined by society, perhaps after some bargaining with a physician's association or union.

At present the need of society for its physicians or the need of physicians for society seems not to be clearly recognized by either. We see society trying to solve many basic problems of health and medical care without seeking any significant input or advice from experienced physicians or their organizations, and we see many of these physicians and many of their organizations taking the attitude that society has fallen into evil ways and that the profession had best remain aloof and uncontaminated by its disease and disorder. Both of these attitudes of course overlook and even ignore milleniums of tradition and human experience. Society has always called upon those whom it believed had the best knowledge and understanding of health and its derangements for advice and help, and physicians have traditionally always responded to sickness wherever it was. To be sure, the thought of personal contamination will and should cause a physician to take whatever measures are immediately available to protect himself, but it is not in the tradition of medicine to withhold or withdraw services or advice from the scene of illness or contamination however unpleasant or evil it may be.

In this kind of context, society always has been and always will be the physicians' patient. At this moment in the history of this country the medical profession is on test. Society still has free choice of physician. It will choose the profession or group from among its members that satisfies its needs and assign to it the role of physician. It is in the best interest of all concerned that the medical profession satisfy these needs. The profession should act promptly and with empathy. Society needs its physicians, and vice versa.

—MSMW

No-Fault Insurance in Medicine

As a collateral development in the general swell of enthusiasm for no-fault insurance as applied to damage in motor vehicle accidents, many physicians and lawyers and insurance people have given attention to adapting the no-fault principle to the settlement of damage claims related to medical treatment.

In this issue of California Medicine, a searching analysis of the problems that no-fault might be expected to solve and the possibility of applying it is made by Dr. David S. Rubsamen, a practicing physician who has had training in law and who writes with uncommon clarity. Dr. Rubsamen picks his way through the intricacies and complexities of disagreements between patient and physician over adverse results of treatment, and at each turn of thought comes to new dilemma. He pursues many an avenue, only to find that in present circumstances no-fault insurance in medicine probably would not do away with the adversary proceedings of malpractice actions which now are so traumatic to physician and patient alike, so financially burdensome and so uneven in application. Rather, he finds, no-fault would seem only to lead circuitously to adversary proceedings of a different order and in a different setting, but quite as unhappy.

What Dr. Rubsamen has done is the very worthwhile job of stating the problem about as clearly as that can be done. And with that as beginning, we may hope that he and others of analytic bent and practical sense can in time work out the infinite refinements and variations that can make no-fault insurance applicable to the practice of medicine.

Howard Hassard
Legal Counsel
California Medical Association

CASE REPORTS

Refer to: Werner SB: Coccidioidomycosis misdiagnosed as contact dermatitis. Calif Med 117:59-61, Jul 1972

Coccidioidomycosis Misdiagnosed as Contact Dermatitis

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ERYTHEMA NODOSUM AND erythema multiforme are hypersensitivity reactions widely known to occur after infection with Coccidioides immitis, and these appear in about 20 percent of symptomatic cases.[1] These cutaneous syndromes occur in many other diseases as well and invite differential diagnostic possibilities.[2] There is little appreciation, however, of another cutaneous lesion of acute coccidioidomycosis which does not denote specific sensitivity to the fungal agent and which, when it occurs, does so at the outset of symptoms rather than two or three weeks later as is the case with erythema nodosum and erythema multiforme. This early lesion has been described as a generalized, erythematous, fine macular eruption simulating "toxic erythemas" of other acute febrile illnesses. Occasionally, it is urticarial or morbilliform.[1]

The purpose of this report is to alert physicians to the possibility of coccidioidomycosis in patients from endemic areas who present with influenza-like symptoms *and* co-existing rash. The rash may even be the chief complaint, as discussed below.

One of the largest outbreaks of coccidioidomycosis ever reported from a common point source and confirmed by soil cultures occurred in July, 1970, in Northern California.[3] The outbreak occurred among 103 archaeology students digging for Indian artifacts 9 miles northeast of Chico in the foothills of the Sierra range. This site was 70 miles northeast of previously documented northern limits of endemicity for coccidioidomycosis. Sixty-one persons developed an illness clinically compatible with coccidioidomycosis, and rash occurred in 30 of them or 49 percent). A previous report estimated the occurrence of rash in patients ill with coccidioidomycosis at 10 percent.[1] Except for two persons with "poison oak," all who had rash also had other symptoms of coccidioidomycosis, such as cough or chest pain. The California State Department of Public Health and other agencies collaborated in the investigation of the outbreak.[3]

Case histories of two persons are of special interest because both were initially thought to have contact dermatitis but were found by laboratory studies to have coccidioidomycosis.

Reports of Cases

Case 1. A 19-year-old white male student from New York City, who had never before visited areas endemic for coccidioidomycosis, arrived in Chico, California, June 14, 1970. On June 17, he began excavating for Indian ruins and on July 2 began to complain of a generalized, pruritic, urticarial, maculopapular eruption. On July 6 he presented at the college infirmary, where "urticaria" was diagnosed. An antihistamine and topical corticosteroids were prescribed. As symptoms did not improve, he consulted a private physician on July 11 and was admitted to hospital that day. Only cutaneous symptoms were reported in the admission history. Physical examination was

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Submitted July 30, 1971.

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reported to be unremarkable except for temperature of 38.6°C (101.6°F) and a diffuse, generalized, confluent rash of varying intensity.

The hematocrit was 50 percent and leukocytes numbered 19,000 per cu mm (differential count: 11 percent bands, 74 percent segmented cells, 11 percent lymphocytes, 2 percent monocytes, and 2 percent eosinophils). Blood culture was sterile. Urinalysis was unremarkable except for 4 to 5 white blood cells per high power field. Urine was sterile on culture. No chest x-ray film was taken.

The nurses' notes recorded other complaints: "He aches, has chills, and feels weak." The admitting diagnosis was "allergic dermatitis of unknown etiology," and he was treated with epinephrine, an antihistamine (Benadryl®), calamine lotion, and prednisone 5 mg four times a day. He was discharged on July 15 with a diagnosis of "contact dermatitis." Outpatient therapy of dexamethasone (Decadron®), one 0.75 mg tablet three times a day, was provided.

In a mass survey[3] conducted 15 days after onset of his rash, this patient indicated on a questionnaire additional symptoms of shaking chills, malaise, and chest pain. On examination a generalized, confluent, macular rash and circumoral pallor were noted. The patient had a coccidioidin skin test reaction of 17 mm of induration and positive precipitin reaction with C. immitis antigen. A posterior-anterior chest x-ray film revealed bilateral lower lobe pneumonia (Figure 1). The patient was lost to follow-up on his return to New York City.

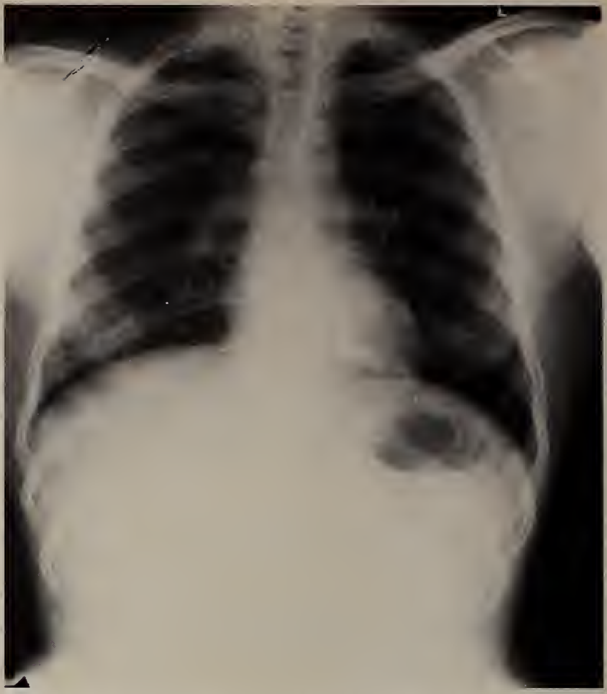

Figure 1.—(Case 1) 19-year-old white male with bilateral lower lobe pneumonia.

Case 2. A 21-year-old white co-ed from New York who also had never been in areas endemic for coccidioidomycosis arrived in Chico, California, on June 14, 1970. She began digging at the excavation site one day later. On July 11 she became ill, and on July 13 was put into hospital by a private physician. Her admitting history reported a generalized, confluent pruritic rash and "some little discomfort in her chest." On physical examination she had a temperature of 37.8°C (100°F) and a rash which was quite raised in areas. She appeared healthy otherwise.

The admitting diagnosis was "contact dermatitis . . . due to something [she is] doing in school." Laboratory data included a hematocrit of 40 percent and leukocyte count of 13,900 (differential count: 70 percent segmented forms, 3 percent bands, 21 percent lymphocytes, 4 percent monocytes, and 2 percent eosinophils). A urinalysis was negative except for 5 to 7 white cells per high power field. No chest x-ray film was taken.

Therapy as an inpatient included epinephrine, dexamethasone (Decadron®), an antihistamine (Benadryl®), and starch baths. The patient was discharged July 15 with Benadryl and Decadron, one 0.75 mg tablet three times a day.

At the mass survey conducted on July 17, she reported that she began having chest pains and shortness of breath on July 8, and on July 11 developed fever, shaking chills, headache, myalgia, stiff neck, night sweats, cough, and the rash described earlier. A coccidioidin skin test was positive at 11 mm of induration and a chest x-ray film showed patchy right lower lobe pneumonia (Figure 2). The patient recovered fully. Her initial symptoms lasted about one week and there was a "slight relapse of chest pains and shortness of breath for a few days in September." She reported that she had been "fine" since then.

Discussion

Both cases illustrate the need to consider coccidioidomycosis in the differential diagnosis of respiratory illness *and* co-existing rash in persons from endemic areas especially when there is

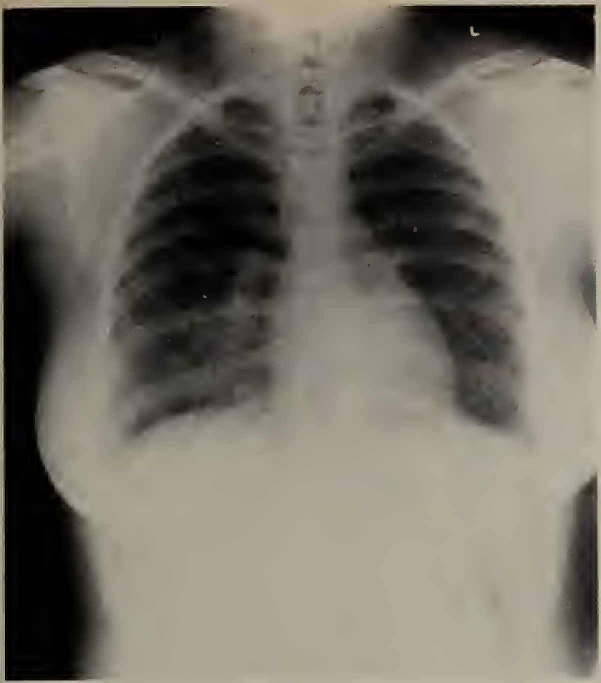

Figure 2.—(Case 2) 21-year-old white woman with patchy right lower lobe pneumonia.

heavy exposure to soil. Even the casual exposure of driving through highly endemic areas such as the San Joaquin Valley has been sufficient for infection by C. immitis.[4] The Chico area was not previously known to be endemic for C. immitis and this probably influenced the diagnostic considerations of attending physicians. Until this outbreak, the most northern area in California and the United States documented to be endemic for C. immitis was 70 miles southwest of Chico near Brooks, California.[5]

Both patients reported upon here were treated with systemic corticosteroids. Caution should be exercised in the use of such therapy for coccidioidomycosis, since subsequent fungal dissemination has been reported.[6] On the other hand, Levan and Einstein did treat 19 cases of Valley Fever with a short course of cortisone without evidence of dissemination.[7] However, persons with "Valley Fever" (that is, primary coccidioidomycosis *with* hypersensitivity reactions of erythema nodosum and/or erythema multiforme) may have a more favorable prognosis with regard to dissemination than those without such hypersensitivity reactions. Indeed, Faber, Smith and Dickson reported that only one in seven hundred with Valley Fever undergo spontaneous dissemination[8] whereas in symptomatic primary coccidioidomycosis this complication occurs in about 1 percent of white males and in 12 percent of Negro males.[9]

Summary

Nonspecific "toxic erythema" is not widely appreciated as a concurrent clinical feature of early primary coccidioidomycosis. Two cases are presented in which cutaneous manifestations were, in fact, the chief complaint. Both patients were admitted to hospital with diagnosis of "contact dermatitis" and were treated with systemic corticosteroids. The attendant risks are mentioned. The existence of a generalized, pruritic, maculopapular eruption in patients with influenza-like symptoms coming from endemic areas should alert physicians to the possibility of coccidioidomycosis.

ACKNOWLEDGEMENT: Serologic studies were performed at the Microbial Diseases Laboratory, California State Department of Public Health and at the Department of Medical Microbiology of the University of California, Davis, School of Medicine. Survey of the archaeology class was made possible by Irena Heindl, M.D., Health Officer of Butte County Health Department, and Arthur Mickel, M.D., Student Health Service, Chico State College.

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Refer to: Irvin LA, Neal RM, Wilkening DL, et al: Laparoscopic removal of ectopically lodged intra-uterine devices. Calif Med 117:62-63, Jul 1972

Laparoscopic Removal of Ectopically Lodged Intra-Uterine Devices

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AS LAPAROSCOPY BECOMES an accepted and frequently used diagnostic and therapeutic tool, new applications of its use appear. The removal of an extra-intrauterine contraceptive device (IUCD) from lodgement in an extra-uterine intra-abdominal space has been reported,[1,2,3] and three cases herein described add additional significance to this simple treatment of a common complication of the use of such contraceptive devices. The low morbidity associated with laparoscopy suggests an attempt at removal by laparoscopy of an intra-abdominal intra-uterine contraceptive device in preference to laparotomy. The following three case reports illustrate this approach.

The laparoscope is similar to a modern fiberoptic cystoscope. It consists of a telescopic optical system surrounded by glass fibers which transmit light into the peritoneal cavity. Thus "cold" light only is used. We use a laparoscopy technique almost identical to that described in the third chapter of Cohen's book *Laparoscopy, Culdoscopy and Gynecography*.[4] Essentially, the procedure is to establish a 4-liter carbon dioxide pneumoperitoneum after the patient has been anesthetized, catheterized and surgically prepared. This pneumoperitoneum is introduced through a Verres needle inserted through a small periumbilical skin incision. Following the establishment of the pneumoperitoneum, a 10 mm trocar covered by a metal sleeve and valve is introduced into the peritoneal cavity through the same incision. The trocar is replaced by a 10 mm Wolf laparoscope. After inspection of the abdominal contents, the operative instruments are introduced through a 6 mm sleeve placed in the right or left lower quadrant. It is through this secondary opening that operative instruments for tubal sterilization and instruments for biopsy and manipulation are introduced. In addition to the cases reported here, we have used laparoscopy for tubal sterilization in 200 cases; for ovarian and directed liver biopsy; for biopsy of peritoneal and pelvic metastatic cancer; for diagnosis in Turner's syndrome and ovarian agenesis; for observation of uterine perforations; and for confirmation of questionable ectopic pregnancy.

Case 1. A 19-year-old woman, gravida II, para II, was seen 9 October 1970. She had had a Lippe's loop inserted without difficulty, in August 1969 at the time of an examination six-weeks postpartum. The patient's menses were regular until October 1969, when she became pregnant. The prenatal course was normal and the baby was delivered 21 July 1970. The IUCD was not delivered at this time and could not be found on exploration of the endometrial cavity. A hysterosalpingogram on 23 October 1970 was reported as showing "extra-uterine left anteroretropubic position of contraceptive ribbon type device."

The patient was admitted to Kern General Hospital's gynecological service 14 September 1970. The uterus was normal in size and position and the adnexa were also normal. Laparotomy for removal of the device was considered but it was decided to try first to retrieve it through laparoscopy. The procedure was carried out with the patient under general anesthesia and the omentum was found to be adhesed in the anterior pelvic cul-de-sac. By manipulation of a Jarcho cannula that had been placed beforehand, the fundus of the uterus could be visualized through the omentum and the Lippe's loop was indistinctly seen in the left anterior retropubic location. A probe was placed through the secondary trocar. Blunt dissection with the probe was accomplished without bleeding, until the tip of the device was freed and could be grasped with the electrocautery forceps. Finally it was lying free in the peritoneal cavity and was removed through the secondary trocar sleeve. The patient was discharged 18 hours later.

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Case 2. The patient, 25 years of age, gravida II, para II, was admitted to the gynecologic service 12 May 1969 with complaint of premenstrual fever and abdominal pain of three months' duration. She said that she had also had intermittent abdominal pain two years previously after insertion of a Lippe's loop. No abnormality was noted on pelvic palpation. An x-ray examination showed an IUCD with slight deformity suggesting intramural lodgement of the device. Laparoscopy was done to determine the location of the IUCD and for tubal cauterization, which was performed. The longest arm of the loop was observed perforating the right posterior uterine wall. It was removed transvaginally under laparoscopic observation. The patient was asymptomatic and was discharged on the second postoperative day.

Case 3.[*] The patient, 21 years old, gravida II, para I, had had a therapeutic abortion by suction curretage in June 1971, and four weeks later a size C Lippe's loop was inserted without pain or other difficulty. She had had regular periods and was able to palpate the string attached to the loop. Her last period, beginning 5 September 1971, was associated with severe cramping and heavy bleeding. Following the period the patient was unable to feel the IUD string, and it was not visible at the cervix on examination. An x-ray film showed the IUD in the pelvic area. Peritoneoscopy was performed 14 October 1971 and the device was seen to be interwoven in the tip of the omentum in the pelvis. It was grasped and removed without difficulty through the secondary trocar. The patient did well postoperatively, and was discharged on the first postoperative day.

Summary

Intra-uterine contraceptive devices that had lodged at extra-uterine sites in the abdomen were successfully removed by laparoscopy in three cases.

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[*] Presented through the courtesy of Larry C. Hubbell, M.D., Bakersfield, California.

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Refer to: Weinraub M, Groce P, Karno M: Chloroformism—A new case of a bad old habit. Calif Med 117:63-65, Jul 1972

Chloroformism—A New Case of a Bad Old Habit

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NITROUS OXIDE, ETHER AND chloroform were the three, volatile, anesthetic agents which launched the history of surgical anesthesia in the first half of the nineteenth century. Although the "Scottish chloroform legend"[1] allegedly minimized the dangers of chloroform, it was that agent which produced the first recorded death under anesthesia, when administered to a 15-year-old English girl before the intended removal of an ingrowing toenail in the year 1848.[2]

Chloroform was also the agent self-administered by Horace Wells, one of the pioneers of anesthesia, as a prelude to his suicide in a New York prison at the age of 33, also in 1848. The week before his suicide, Wells had reportedly become increasingly dependent on chronic chloroform usage: "Day after day during that week he inhaled more and more from his chloroform bottle. Then the break came. He ran completely amuck and was arrested."[3]

The continued acceptance and use of chloroform in England was undoubtedly bolstered by Queen Victoria's reliance upon it during the birth of her eighth child, Prince Leopold, in 1853.[4]

There are scattered allusions in the literature to the "frolics," "sprees" and "jags" of medical students and others who used volatile anesthetics for pleasure during the 19th century. A first person account by a young man who had become a "chloroform fiend" was read by his physician to the Detroit Academy of Medicine in 1885: "It is

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The senior author was a fourth year medical student, University of California, San Diego, at the time this paper was submitted.

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a heaven of chaste pleasures. What I most remember is the vivid pictures that would seem to pass before my eyes — creations of marvelous beauty—every image distinct in outline, perfect in symmetry and brilliant in coloring. The enjoyment is purely passive; you have only to watch vision after vision. . . . I felt no craving for my pet intoxicant during the day—did not give it a thought often until bed time came, and then it would occur to me for a moment to try and see how it would seem to go to sleep in the ordinary way, the conclusion always being that—tomorrow night I would make the experiment."[5] The Academy also heard another physician present a series of case reports of chloroformomania, the victim of which ". . . finds his digestion impaired, circulation impeded, locomotion affected, correlation of ideas impossible, virility lessened, and a complete demoralization of both body and mind tending to a morbid condition, the only relief from which is the insensibility produced by chloroform, thus adding fuel to the fire and eventually ending in syncope and sudden death."[6]

Chloroformism has been reported very rarely in recent years, although in 1945, a case was described from the Menninger Sanitarium of a schizophrenic man, an alcoholic, who had also become dependent upon chloroform.[7] With the widespread current press accounts of the many inhalant substances (particularly in aerosol preparations) with which young people today experiment for pleasurable results, it is hardly surprising that we have encountered a young adult with a history of severe and prolonged chloroform habituation.

Report of a Case

A 24-year-old, married, white, U.S. Navy enlisted man was seen 2 April 1971 on self-referral at the University and Fifth Service of the University of California at San Diego Department of Psychiatry with the presenting complaint that he was addicted to chloroform and wanted medical-psychiatric assistance in getting rid of his addiction and in finding out if he had suffered any damage from it. He said that he had begun using chloroform at the age of seventeen while a senior in a private boarding high school. He obtained the chloroform from the chemistry laboratory and used it about 15 times that year to put himself to sleep at night. During college his usage increased to the point where he felt he was "psychologically addicted and couldn't sleep without it." By reading textbooks on chloroform he became expert enough to take elaborate precautions against hypoxia and overdosage. He denied using it to calm nervousness or to get high. After graduation from college, he was using about one gallon of chloroform every six months for sleep but was able to hold a responsible sales job. At age 23 he began active military service. Because of "boredom" his usage increased sharply "to make time fly" until discharge, and he used chloroform regularly, morning and night. With heavy, steady usage on weekends he began to enjoy a "high" during the six months before admission, and was consuming two gallons of chloroform every two weeks during that period. He said, however, that he would spill a significant amount while intoxicated.

A typical day would consist of his inhaling about 5 to 10 ml of chloroform from a small wide-mouth plastic bottle after work. He would then briefly nap, eat and take another dose for sleep. He would usually awaken about 4:00 a.m. when he would take another dose. In the morning he would be a bit groggy but otherwise he would feel fine and would bicycle to work. He has not used chloroform during the work day, but on weekends uses 5 to 10 ml every two or three hours and thus is usually in a twilight state during weekends. While on a week's vacation just before admission, he was using chloroform continuously and was troubled by paresthesias, restlessness, body aches and occasional vomiting. Several times his wife found him gagging while comatose.

His past history was quite unremarkable. He is one of four children; the other three are alive and well. They grew up in a strict, mid-western farm-community and the patient was a "model son" and a good student. He majored in chemistry and graduated in business administration. Before being drafted he was making $16,000 a year as the sales manager of a business firm. He has been married for one year, without reported difficulty. His wife is a laboratory technician. When she learned of his drug use (after they were married), her concerns were assuaged by his assurances that he could stop anytime he wished. His past medical history was not extraordinary except for "prostatic congestion" treated by prostate massage. He denied the intake of any drugs other than chloroform. His physical complaints, other than those mentioned, consisted only of a dry nasal mucosa which bled easily (presumably secondary to his habit) and frequent watery diarrhea.

Psychiatric examination revealed an intense, talkative, neatly and conservatively dressed and groomed young man with moderate hyperactivity and pressure of speech. He overexplains, overcontrols, and is very self-centered. He demonstrates no evidence of psychosis, affective disorder, or deficiency in memory or thinking. Results of a complete physical examination, including neurological and rectal examinations, were within normal limits.

The patient was admitted for detoxification on the day first seen, and was placed under close observation. During the first 36 hours after withdrawal he experienced mild cramping and paresthesias in his limbs, but was thereafter asymptomatic. He received only diazepam (Valium®) 10 mg at night, for sleep. After three days he was discharged with prescription of Valium, 2.5 mg as needed for sleep. Urological consultation revealed no genito-urinary disease.

Blood cell count, urinalysis, bromsulfalein test, glucose tolerance, blood urea nitrogen, creatinine, uric acid, serum calcium, electrolytes, bilirubin, amylase, lactic dehydrogenase, alkaline phosphatase, cholesterol and protein-bound iodine determinations, as well as chest x-ray films and an electroencephalogram were all within normal limits. A VDRL test was non-reactive. Prothrombin time for the patient was 12.5 seconds; for the control, 10.8 seconds. Partial thromboplastin time for the patient was 36.0 seconds; control, 28.0 seconds. SGOT was 67 units (8 to 40 units normal range), and SGPT was 41 units (5 to 35 units normal range). Serum electrophoresis values (grams per 100 ml) were:

- Albumin 5.1 (3.5 to 5.5 normal range)
- Globulin 1.5 (2.6 to 3.8 normal range)
  - alpha-1 0.2 (0.2 to 0.4 normal range)
  - alpha-2 0.3 (0.5 to 0.9 normal range)
  - beta 0.4 (0.6 to 1.1 normal range)
  - gamma 0.6 (0.7 to 1.7 normal range)

Follow-up

The patient felt confident that he could maintain himself on a drug-free status and declined to enter psychotherapy. Follow-up contacts two weeks after discharge and four months after discharge revealed that he was working, sleeping without difficulty, taking no drugs whatsoever, and felt no need for further professional assistance. Repeat laboratory examination four months after discharge revealed normal liver enzyme levels, a normal prothrombin time, but a still elevated partial thromboplastin time (patient, 37.2 seconds; control, 28.8 seconds) and a still low serum globulin level (1.9 grams per 100 ml).

Summary

A 24-year-old man who was chonically and increasingly habituated to chloroform for seven years reached the point, six months before seeking help, of morning and evening usage every day with near steady state intoxication on weekends, culminating in a state of steady intoxication during the week before voluntary admission to hospital for detoxification. After three days of hospital care during which chloroform was immediately discontinued and only small doses of diazepam were given, he was discharged free of symptoms. At one month and four month follow-ups he was functioning well without drugs of any kind. Despite the known hepatotoxicity[8,9] of chloroform, and the degree, duration and tenacity of his habituation, he was found to have only borderline indications of hepatic dysfunction and minimal psychopathology.

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Refer to: Sokol AB, Morgenstern L: Gastric volvulus complicating paraesophageal hiatal hernia. Calif Med 117:66-69, Jul 1972

Gastric Volvulus Complicating Paraesophageal Hiatal Hernia

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Gastric volvulus complicating a paraesophageal hiatal hernia is rare.[1,2] Because the threat of strangulation and infarction of the incarcerated stomach is great, prompt recognition and surgical correction of this condition is mandatory. Two cases occurring within a 14-day period at the Cedars-Sinai Medical Center prompted this review.

Reports of Cases

Case 1. A 68-year-old white woman with a known paraesophageal hiatal hernia had sudden onset of severe midepigastric pain during dinner. It radiated to the umbilicus and the back, remained steady and severe and was unrelieved by change of position or by taking food. When first seen in the hospital, she was restless and was noted to be obese. Despite complaint of severe abdominal pain, abdominal findings were negative. Attempts at passing a nasogastric tube were unsuccessful. An x-ray film of the chest showed double fluid levels and de Lorimier's hair pin loop with incisura directed toward the right upper quadrant (Figures 1 and 2). Two hours after admission a mass became palpable in the epigastrium and the patient was taken to surgery. At operation gastric volvulus was observed and the stomach, which had herniated through a 10 x 15 cm diaphragmatic defect, was incarcerated in the left side of the chest. As the patient's cardiovascular status began to deteriorate during the operation, as manifested by low blood pressure and irregular pulse, simple reduction of the volvulus was carried out without repair of the hiatal hernia. The postoperative course was complicated by a left pleural effusion

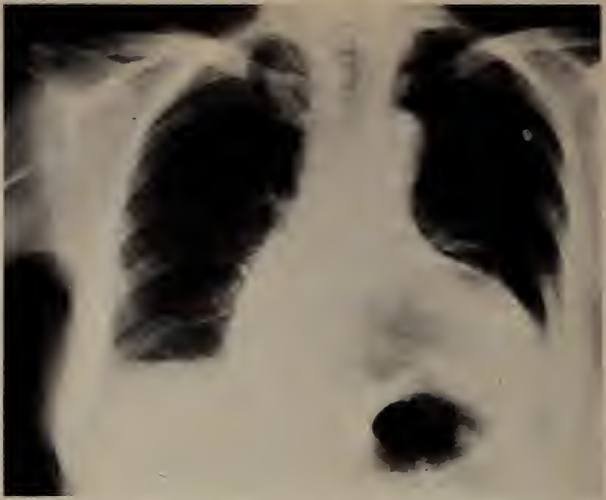

Figure 1.—(Case 1) Film of chest showing a double air level, one above and one below the diaphragm. This condition occurs when the fundic portion of the intrathoracic stomach redescends into the abdomen, leading to a closed loop phenomenon. Note the "hairpin loop" sign with the incisura directed toward the right upper quadrant.

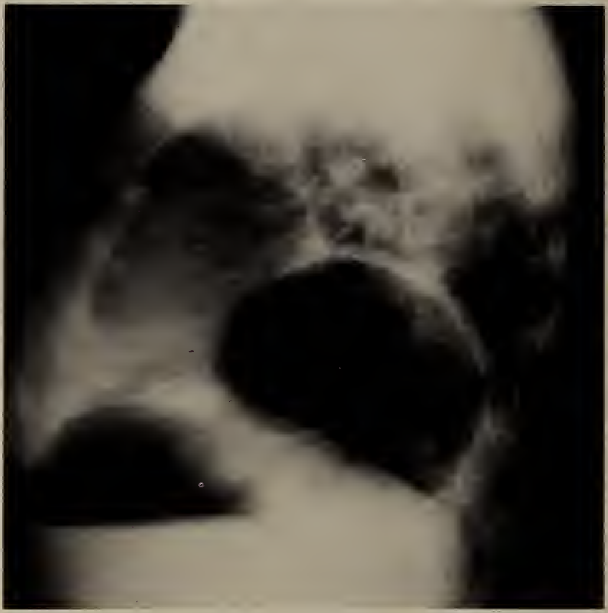

Figure 2.—Lateral view of the chest better demonstrating the double air fluid level shown in Figure 1.

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but was otherwise unremarkable. She became asymptomatic and elected not to undergo further operation.

Case 2. A 63-year-old white man entered the hospital with history of several days of persistent vomiting and abdominal pain with radiation to the back and lower left anterior chest, unrelieved by change of position or by antacids. There was a ten-year history of an "upside-down stomach." The patient appeared acutely ill, as characterized by anxiety, ashen facies and restlessness. He was severely dehydrated and complained of abdominal pain. There were no other significant physical findings. Laboratory work-up revealed severe hypochloremic, hypokalemic alkalosis, and hypovolemia. Upper gastrointestinal x-ray studies revealed gastric volvulus with a portion of the fundus incarcerated in the chest (Figure 3). After 48 hours, the fluid and electrolyte imbalance had been sufficiently corrected to permit operative intervention. At operation, because of labile blood pressure, the herniated cardiac and fundic portions of the stomach were simply reduced, as they appeared viable, and gastrostomy was performed. Eleven days later an operation for definitive transabdominal repair of hiatal hernia was carried out.

Symptoms of Acute Volvulus

Historically, the acute obstruction occasioned by volvulus usually begins not long after a meal, but it may awaken the patient from sleep. Usually there is history of several previous episodes that were relieved by non-specific measures.[3,4,5,6]

The patient complains of sudden epigastric or left lower thoracic pain with radiation through to the back, unrelieved by change of position. Associated with the pain are unsuccessful attempts at vomiting and symptoms of high gastrointestinal obstruction. On physical examination, although the patient is acutely ill, restless and complaining of severe pain, there are usually no actual physical findings, with the infrequent exception of possible tympany of the left lower thorax or a mass in the epigastrium. If the volvulus persists and does not spontaneously reduce, signs of cardiovascular collapse occur secondary to gastric infarction and progressive hypovolemia associated with diminished intake and the interstitial sequestration of fluid within the walls of the infarcted thoracic stomach.[4,7]

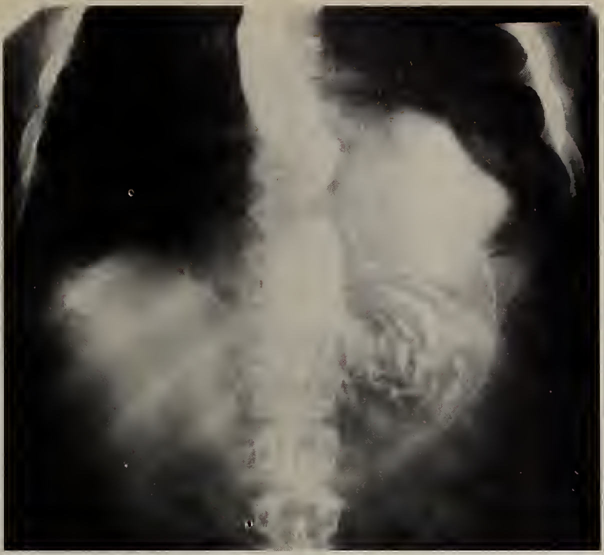

Figure 3.—(Case 2) Selected view from an upper gastrointestinal series demonstrating several signs of gastric volvulus. Note the rotation seen best by the rugal folds of the body radiating toward the lesser curvature. One can see the virtually complete pyloric obstruction secondary to the rotation, and edema is manifested by the lack of contrast material in the duodenum. Finally, note the vague shadow of contrast material in the chest which represented the incarcerated fundic portion of the stomach.

Diagnosis

Radiologic examination is diagnostic. Films of the chest or abdomen may demonstrate a high "simulated" left diaphragm which is actually the herniated and distended greater curvature of the stomach. Double air fluid levels occur if (as in Culver's cases and our own Case 1) the fundic portion of the thoracic stomach redescends into the abdomen.[4] There may be a "hairpin" loop with the incisura directed toward the right upper quadrant or posteriorly. Massive gaseous distension in the upper abdomen or chest may appear, with a gas bubble on either side of the midline. Barium swallow studies demonstrate the classic signs of volvulus, such as sharp cut-off of the esophageal or gastric barium column, abnormal twisting of rugal folds, and finally delineation of the intrathoracic portion of the stomach.

Feldman and de Lorimier's articles give excellent reviews as to the roentgenographic signs of gastric volvulus.[8,9,10]

Attempts at gastric intubation are either met with resistance due to obstruction at the esophagogastric junction or with initial relief of abdominal pain due to expulsion of great quantities of gas, only to be followed by progressive and per-

TABLE 1.—*Data on Eight Patients with Paraesophageal Hiatal Hernia* (PEHH)

Patient	*Age*	*Sex*	*Admission Date(s)*	*Symptoms of* PEHH	*Dx*	*Therapy and Findings*
1.	76	M	1965	Intermittent obstruct. assoc. with chest pain relieved with emesis	X-ray	Antacids for PEHH
2.	61	F	May 1963	Constricting chest pain	X-ray	Antacids for PEHH with partial incarceration of gastric fundus
			Aug 1963	Progressive abd pain, emesis for 3 days	Oper.	Operative reduction of a gastric volvulus with resection of an area of necrotic gastric fundus and repair of hiatal hernia
3.	73	F	1965	Epigastric gas and burning assoc. with meals	X-ray	Antacids for PEHH with esophagitis
4.	37	F	1962	Persistent chest pain and emesis	X-ray	Operative reduction of incarcerated PEHH containing stomach
5.	71	M	1962	Abdominal pain and gas	X-ray	Antacids for PEHH
			1963	None	Oper.	Resection of transverse colon
6.	36	F	Nov 1963	Regurgitation with bending over	X-ray	Operative repair of incarcerated PEHH
			Oct 1964	Recurrent symptoms	X-ray	Operative repair of recurrent incarcerated PEHH
7.	62	M	1963	Epigastric pain and nausea	X-ray	Antacids for PEHH
			1963	Persistent symptoms	Oper.	Operative reduction of incarcerated PEHH consisting of 50 percent of the stomach and the spleen. Because of high gastric acids, a P & V was performed in addition to repair of the hiatal hernia
8.	63	F	Feb 1963	None	X-ray	Antacids for bleeding duodenal ulcer
			Nov 1963	None	X-ray	Antacids for bleeding duodenal ulcer

sistent signs of the volvulus. Borchardt's and Lenormont's triad — unsuccessful vomiting, circumscribed epigastric pain, and inability to pass a tube into the stomach in a patient with a known paraesophageal hiatal hernia should make one suspect this dire complication.[1,4]

Treatment

Upon diagnosing gastric volvulus, operation should be performed immediately or after the least possible delay for correcting the associated fluid and electrolyte imbalance. Following reduction of the volvulus, definitive repair of the hiatal hernia will depend upon the clinical status of the patient.

The mortality of gastric volvulus is 40 percent, usually due first to lack of recognition and consequent profound cardiovascular collapse and second to the pneumonitic process which occurs from the intrathoracic infarcted stomach and repeated aspirations of esophageal secretions or foodstuffs.[1,2,5,10]

Incidence in Persons With Hiatal Hernia

During a five-year period, 77,231 patients were admitted to the private service of the Cedars of Lebanon Hospital. Of the 274 who were admitted for hiatal hernia, 206 had the sliding variety, 13 paraesophageal, and one the congenital type; fifty-four admissions were for "undiagnosed types" of hiatal hernia. In this category are included cases that could not be classified in the above categories after review of charts, radiographic reports and operative findings.

Discussion

The patients with the sliding type were found most frequently to have symptoms relating to reflux esophagitis and bleeding. Those with paraesophageal hiatal hernia usually had obstructive symptoms (Table 1). While symptoms were mild in about half the cases of sliding type, they were severe in more than 75 percent of the paraesophageal type and 50 percent of the patients required operation.

Operative repair of paraesophageal hiatal hernia is recommended at its earliest stage whether symptoms exist or not.

Summary

Two cases of paraesophageal hiatal hernia were complicated by gastric volvulus. A distinct symptom complex occurs with obstruction and is associated with diagnostic radiographic criteria.

Of two hundred and seventy-four admissions to Cedars of Lebanon Hospital for hiatal hernia during a five-year period, thirteen were for paraesophageal hiatal hernia. Nine of the patients had symptoms and four required surgical repair.

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Primary Amebic Meningoencephalitis In California

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PRIMARY AMEBIC MENINGOENCEPHALITIS, to be distinguished from infections caused by Entamoeba histolytica, is a newly recognized disease entity. The infrequently encountered causative organism is usually a ubiquitous, free living, soil ameba of the Naegleriidae family (species Naegleria). The first cases were reported in 1965 from Australia[1] and since then, to our knowledge, 54 cases have been documented. In the United States, the disease has been detected in Florida,[2,3] Texas,[4] Virginia[5,6,7,8] and Georgia.[9] Elsewhere, this diagnosis has been made in Australia,[1,10] Czechoslovakia,[11,12] Britain,[13] Ireland,[13] New Zealand[14] and Africa.[15] This account will document the first reported occurrence of primary amebic meningoencephalitis in California and will describe its clinical, epidemiological and pathological characteristics. Furthermore, the entity will be reviewed to acquaint others with this rapidly fatal disease in order that it will be promptly recognized and early vigorous attempts at appropriate therapy undertaken. In addition, as new cases are recognized, measures should be instituted to prevent further outbreaks.

Report of a Case

A 16-year-old caucasian girl was admitted to Harbor General Hospital on April 29, 1971, with

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complaint of headache and nuchal rigidity of one day's duration. Five days before admission, on a week-end day, she swam in a remote desert valley hot spring near San Bernardino, California (in the southern Sierra Nevada mountains). The night before swimming, the patient had become intoxicated with alcohol and vomited. She returned home and was well until four days later, when she awoke with severe frontal headache. Nuchal rigidity ensued along with photophobia, mild sore throat, fever, chills, sweats, mild arthralgias, myalgias and nausea. She had not noted earache or change in taste or smell.

Her past history revealed excellent health and she denied head trauma. While swimming, she was accompanied by several friends, none of whom had similar symptoms.

On physical examination, body temperature was 40° C (104° F), pulse 98 rate and respirations 24 per min, and blood pressure 140/80 mm of mercury. She was alert, well developed and well nourished. The neck was decidedly rigid and Brudzinski's sign was evoked. The right tympanic membrane was minimally injected but was otherwise not unusual; the left tympanic membrane was normal. The nasal mucosa appeared normal. No abnormality was noted on examination of the heart, lungs and abdomen. There were no skin lesions or adenopathy. Funduscopic examination showed no abnormality. There was mild conjunctival injection. Neurological examination was significant in that there were no lateralizing signs, cranial nerve abnormalities or pathological reflexes.

Laboratory data on admission showed hematocrit of 39 percent, leukocytes 12,600 per cu mm with 80 percent polymorphonuclear leukocytes, 2 percent band forms, 15 percent monocytes and 3 percent lymphocytes. With the exception of trace proteinuria, the urinalysis, platelet count, prothrombin time, partial thromboplastin time, fibrinogen, serum electrolytes, blood urea nitrogen, calcium, bilirubin, SGOT, LDH, alkaline phosphatase, total protein and albumin were all normal. A mono-spot test was negative, and skull and chest roentgenograms were interpreted as normal. On lumbar puncture the opening pressure of 280 mm of water. The fluid, which was slightly cloudy, contained 310 leukocytes per cu mm (68 percent polymorphonuclear, 32 percent lymphocytes) erythrocytes 90 per cu mm, protein 72 mg per 100 ml, glucose 70 mg per 100 ml (blood glucose of 156 mg two hours earlier) and a negative Gram stain for bacteria. A wet mount examination of the spinal fluid was not performed.

A presumed diagnosis of viral meningoencephalitis was tendered and the patient was kept under observation. Six hours later she became obtund. Eight hours after admission she was comatose, with decerebrate posturing. A repeat lumbar puncture at that time showed pressure of 550 mm of water. Gradual removal of fluid lowered the pressure to 230 mm. The fluid was purulent and contained 3,330 leukocytes per cu mm (78 percent polymorphonuclear and 22 percent lymphocytes), 250 erythrocytes per cu mm, protein of 290 mg and glucose of 82 mg per 100 ml. Blood glucose was 259 mg per 100 ml (the patient was receiving 5 percent dextrose intravenous infusion). Gram and acid-fast stains failed to demonstrate any organisms. Because of rapidly progressive purulent meningitis, ampicillin 2 grams intravenously every four hours was started. There was no significant improvement over the next 48 hours. The temperature increased to 40.6° C (105° F) and leukocytes rose to 20,400 per cu mm of peripheral blood. Sixty hours after admission the patient had papilledema, extensor plantar reflexes and periods of apnea. Despite respiratory support and dexamethasone and mannitol infusions to decrease cerebral edema, she became hypothermic and cardiac arrest occurred. She could not be resuscitated and died four days after admission. Cultures of the cerebrospinal fluid from the two lumbar punctures and blood cultures were negative for any bacterial growth. Viral cultures of the cerebrospinal fluid, nasal and rectal swabs were also negative.

Autopsy Findings

The brain weighed 1,360 grams and there was herniation of the cerebellar tonsils. The leptomeninges, most prominently at the base, were thickened, edematous and opacified. The olfactory bulbs were similarly edematous and the left one was also necrotic (Figure 1). A superficial, hemorrhagic, necrotizing process involved the frontal, parietal and temporal lobes and cerebellum. A small round area of hemorrhage involved the left caudate nucleus.

Microscopically, hemorrhagic, necrotizing, purulent meningitis with some lymphocytes was seen, predominantly in the pons and cerebellum.

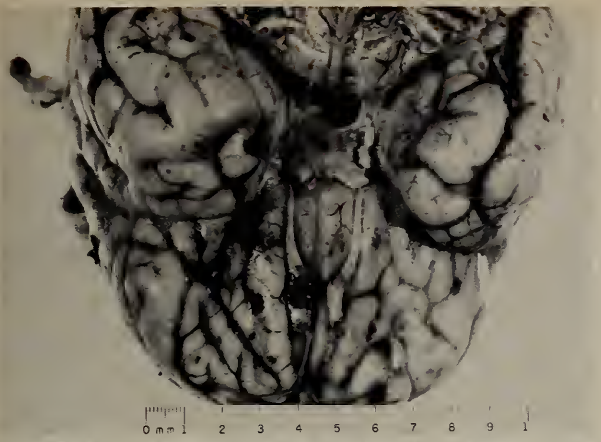

Figure 1.—Appearance of the inferior aspect of the anterior portion of the brain, showing necrotic left olfactory bulb and focal superficial cortical hemorrhages.

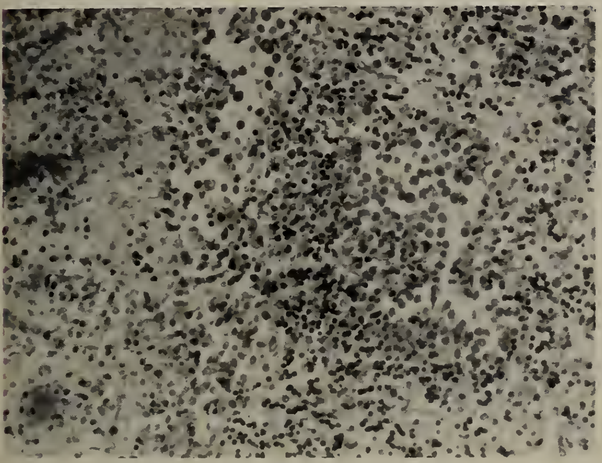

Figure 2.—Cerebellum showing clusters of amebae, virtually without inflammatory response. (Hematoxylin and eosin X550)

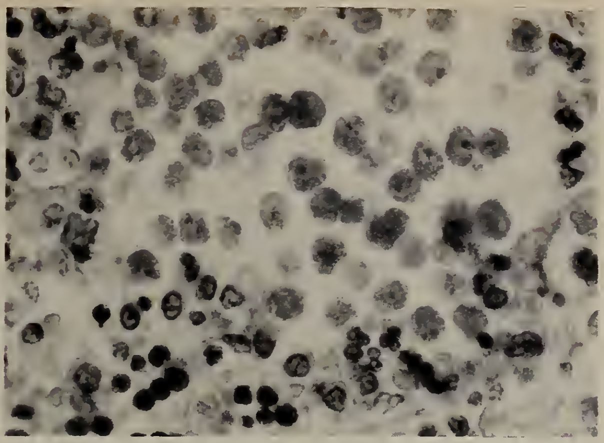

Figure 3.—Detail of Figure 2, showing characteristic morphologic features of the ameba. Note the dark, central karyosome, perinuclear halo and coarse, clumped cytoplasm. (Hematoxylin and eosin X1200)

Extending in the Virchow-Robin spaces, it affected the superficial portions of the underlying brain. Typically, deeper in the brain, clusters of organisms were located in perivascular spaces, remarkably without an inflammatory response in the immediate vicinity (Figure 2). However, microabscesses were scattered throughout the cerebral cortex, some containing clumps of amebae. A few organisms could be seen in the inflamed meninges. With hematoxylin and eosin stain, the ameba were magenta, round, approximately 10 to 12 microns in diameter, and contained a dark, centrally located karyosome surrounded by a thin, clear halo (Figure 3). Some bi-nucleated and tri-nucleated forms were identified. Although other stains, including periodic acid-Schiff, iron hematoxylin, Best's carmine, Masson trichrome, Gram's, silver methename, phosphotungstic acid hematoxylin and Giemsa, were utilized, none proved superior to hematoxylin and eosin for identification and characterization of the organism.

The left olfactory bulb and tract, which contained rare organisms, were virtually destroyed by hemorrhagic necrosis and acute inflammation. The right olfactory bulb and tract were minimally affected. Many small blood vessels in proximity to the inflammation were thrombosed.

The lungs weighed 900 grams together and were edematous. A few small foci of early bronchopneumonia were evident. The kidneys were grossly unremarkable but microscopically showed pronounced hydropic change of the proximal convoluted tubules and cells lining Bowman's capsule. Of anatomic curiosity only was the finding of a well defined muscularis mucosa of the bladder. On detailed examination, amebae were not found in any tissue but the brain.

A suspension of refrigerated brain tissue was injected intracerebrally into mice but in two weeks produced no pathologic changes. Similarly, tissue cultures, utilizing monkey kidney, Hela and Wi 38 cells, failed to demonstrate the amebae. Using methods described by Culbertson et al[25] and Carter,[19] ameba, not well speciated, were cultured from samples of water from the hot springs pool in which the patient swam.

Discussion

The case reported here is similar to cases described by other observers. Classically, primary amebic meningoencephalitis is an overwhelming, rapidly fatal meningoencephalitis that affects a previously healthy child or young adult with a history of recent swimming in fresh-water lakes, brackish water or pools of diverted river water. Of particular interest is a recent report from New Zealand[14] of an outbreak associated with bathing in a mineral spring. This is epidemiologically similar to the case herein reported. In both situations, water of 100° F originated in deep subterranean springs. In our case vegetation around the mineral pool was sparse, but the water had abundant moss and algae on the rock enclosing it. Week-end activities at this desert spring are described as crowded with young men and women bathing nude. Increased environmental CO_2 and bacteria facilitate the excystment and survival of Naegleria gruberi.[25] As a result, crowded conditions at the mineral pool may have enhanced the density of pathogens during the time our patient swam. Why others were not similarly afflicted with the disease remains unclear.

Epidemiologic observations of this disorder unassociated with swimming should be emphasized. Primary amebic meningoencephalitis has occurred in a patient with advanced alcoholic liver disease who had dental extractions.[4] An intriguing report of three cases occurring in children playing in a warm, muddy puddle was recently reported in England.[16] Furthermore, the isolation of Hartmanella species from normal throats has been noted.[17]

The history of swimming in a remote desert hot springs was, unfortunately, unavailable until the day of our patient's death. Nevertheless, the syndrome of primary amebic meningoencephalitis was considered in the differential diagnosis, but was discounted when the typical history of swimming was not obtained. Few cases have been diagnosed antemortem.[16,18] Most have occurred in an area of endemicity or in a setting of other documented cases.[11,18] The diagnosis is invariably confirmed by the finding of motile trophozoites in the cerebrospinal fluid wet mount. Unfortunately, this procedure is not routinely employed in the evaluation of spinal fluid; because of the epidemiologic observations detailed above, it should be a routine examination in any case of meningitis. In this case, retrospective examination of a Gram stain of the cerebrospinal fluid revealed a few identifiable organisms. Culture methods are available to grow free-living amebae in both tissue cultures[20] and on plain agar with live organisms.[19] Recently an agglutination test for Acathameba has been described,[21] in addition to a complement fixation test.[23] Even so, the spinal fluid wet mount remains the diagnostic test of choice.

The pathological findings in the present case were in keeping with those reported by other observers:[6,10] purulent meningitis is associated with a superficial necrotizing and hemorrhagic encephalitis. Basilar meningitis with necrosis of the olfactory bulbs and tracts confirm the suggested pathogenesis of migration of organisms through the nasal mucosa to the olfactory apparatus. While cerebral edema is a usual accompaniment of the inflammation, herniation of the cerebellar tonsils has not, to our knowledge, been emphasized.

Trophozoites in tissue sections have a characteristic appearance. Hematoxylin and eosin stain gives the best results for identification of the organisms, although, as pointed out by many investigators,[8] differentiation of the amebae from gitter cells may be difficult. An awareness of their morphological features and characteristic perivascular distribution, usually without accompanying inflammation, should make histological diagnosis apparent.

The spinal fluid findings in the present case were comparable with those reported by other observers,[10,8,18] but it should be emphasized that the spinal fluid appears more purulent than the cell count might indicate. This may well be a reflection of the number of amebae present. Erythrocytes are invariably present in small to moderate numbers and may correlate with the degree of necrosis and inflammation as can be seen from the pathological specimens. Similarly, hypoglycorrhachia is a feature and may be profound in advanced cases.[18] This would add another entity to the large list of disorders causing low spinal fluid glucose.

Of the patients reported in the literature, only four survived. Acanthamoeba astronyxis was isolated from a child who played in "mud holes and pools of fresh water." This organism was cultured from spinal fluid and the child survived although treated only with ampicillin.[5] Two cases were reported in a mini-epidemic referred to above[16] in which three children played in a mud puddle. After the death of one patient, the two remaining children, who had been similarly exposed, were observed; when meningitis was noted, they were treated with amphotericin B. Amebae were isolated from only one of the two patients who survived. It is debatable whether these represent formes frustes of the disease, as suggested by Symmers,[13] or successful therapy. While motile cells were observed on a few occasions in spinal fluid examinations in the case reported by Grundy and Blowers,[15] the clinical manifestations, chronicity and lack of definite evidence of amebae make a diagnosis of primary amebic meningoencephalitis uncertain. However, because it may well represent a variant of this disorder and because of its apparent response to chloroquine, this case should be noted as one of possible response to therapy.

Susceptibility testing *in vitro* has yielded variable results, probably reflecting difficulty in method. It appears that most organisms are sensitive to amphotericin B,[23,24] and on the basis of a few clinical trials some amelioration of the disease was noted.[23] In cases recognized early, intraventricular and intravenous amphotericin B therapy is suggested.[18] Treatment with metronidazole, chloroquine (with the exception noted above[15]) and emetine has been disappointing. Of interest is the report that suggests *in vitro* antagonism between amphotericin B and steroids.[14] Since most patients are treated with steroids to decrease intracerebral edema, perhaps other measures should be employed instead.

It is apparent that free-living ameba are ubiquitous. Previous cases of amebic meningoencephalitis have occurred in endemic regions (Virginia, Florida, Czechoslovakia, Australia, New Zealand). The case reported here emphasizes that this disease does not necessarily have a localized distribution and that it should be considered in the differential diagnosis of unexplained meningoencephalitis. Furthermore, the organisms should be sought in examination of the cerebrospinal fluid.

ACKNOWLEDGMENT: The authors wish to thank Dr. Ronald Goldman for his aid in the interpretation of the pathological material.

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LETTERS *to the Editor*

Smoking in Hospitals

To the Editor: It is known that tobacco is a poison to the body; that it is the main cause of cancer of the lung. In view of this, what are the hospitals of Sacramento doing to educate the public about these hazards? What are they doing to discourage cigarette smoking? I report the results of a recent personal survey.

The Sutter Hospitals — Large supplies of all brands of cigarettes are sold by the hospital auxiliary in both Sutter Hospitals. Even children beginning at age 15 (the "Candy Stripers") handle and sell these poisons. There is no educational program to discourage smoking.

The Mercy Hospitals — The auxiliary sells cigarettes in both hospitals. There is no educational program to discourage smoking.

The American River Hospital — The auxiliary does not sell cigarettes. The cigarette machine has been moved way back near the psychiatric unit. Apparently psychiatrists and their patients cannot survive without tobacco. Other than a small sign at the bottom of the Information booth in the big front waiting room that states, "Please No Smoking In Patients' Rooms," there is no educational program to discourage smoking.

The Kaiser-Permanente Hospital — They do not sell cigarettes in the hospital but there is heavy cigarette smoking [by some of the personnel]. There is no educational program to discourage smoking.

The Sacramento Medical Center (The County Hospital) — They do not sell cigarettes either through the auxiliary or through machines. Otherwise, they have no educational campaign to discourage cigarette smoking.

The Community Memorial Hospital — Cigarettes are not sold in the hospital either through the auxiliary or through machines. This is the only hospital in Sacramento which prohibits smoking in the waiting room.

The Woodside Hospital — Cigarettes are sold in a machine near the employees cafeteria.

This is the way that the hospitals of Sacramento are failing the people and particularly the youth. The hospitals could do a great deal to discourage smoking:

1. They ought not to sanction cigarette smoking by selling them.
2. Smoking in hospitals should be eliminated.
3. The dangers of smoking should be prominently exhibited on posters throughout the hospital.
4. A continuous, persistent, educational program giving the bad effects of tobacco should be given in each hospital and all employees should be required to attend.

These measures, to improve the health of people, could be carried out if the doctors had the courage to do what they know they should do.

JOHN E. SUMMERS, M.D.
Sacramento

More on Methadone Maintenance

To the Editor: In reply to the letter of Dr. Yehuda Sherman in the April, 1972 issue regarding methadone maintenance, I would take issue with his sources of information, his "facts" and hence his conclusions. It is true that the editorial to which he objects did not mention the rationale for methadone maintenance, but it is Dr. Sherman's conclusion and not that of the editorial that the *only* rationale for this treatment is to reduce the number of crimes.

I believe that the editorial only chose to point out this one facet of the benefits of such treatment to the effect that there is definitely a partial solution to a social problem inherent in what is basically a sound medical treatment of a medical problem. Indeed, if Dr. Sherman has carefully read the report which he cited on the Washington, D.C. study on crime reduction, he would have found out that the actual arrests of those patients in the program dropped to virtually nil, *despite* the fact that the police force was increased from 3,000 to 5,000 officers and *despite* the fact that those very same individuals had spent most of their previous adult lives in jail!

As to Dr. Sherman's statement that the pharmacological benefit of being addicted to methadone is "incidental," I might point out that methadone is not injected (hence all concomitant problems in that regard are avoided), that the desire for heroin itself is decreased, that there is no euphoriant effect (the addict is not "high," is able to drive and has normal reflexes) and that to a large extent the "kick" or other satisfaction from an injection of heroin is neutralized.

Additionally, 60-85 percent of the addicts in various programs are holding down jobs or going to school and are thus rehabilitated members of society.

No one involved in treatment programs sees methadone as a panacea. It is an effective stopgap measure. All efforts to discover other methods of treatment including non-narcotic blocking agents are being encouraged.

I wonder if Dr. Sherman is aware that there are an estimated 30,000 heroin addicts in the Los Angeles County area and that there are over 4,000 on the waiting list for the L.A. County Methadone Maintenance Program—a list which is currently increasing at the rate of 50 per week. Has he considered the feelings engendered by the horrifying necessity of the doctors in those clinics who have to send addicts away from their doors, maybe for years, in essence telling them to go back on the street and continue to get their "fixes" until their names come up on the list? I seriously doubt if Dr. Sherman has spoken to the dedicated doctors involved in the current inadequately funded programs.

Finally, in regard to the suggestion that the prospect of being able to receive methadone would serve to encourage individuals to experiment with heroin, I find this ill-conceived conjecture. Whatever the cause of heroin addiction, there is no evidence that the addict at any time rationally considers the future results of becoming addicted. If he did, he wouldn't start in the first place, since he is surely aware of the results of addiction. Further, the methadone maintenance programs have regulations regarding the length of time one has been addicted to heroin before he may be admitted (usually at least two years). Does Dr. Sherman think that a person who would not try heroin under "normal" circumstances might decide in advance to become addicted in the vague hope that after two or three years he could get on the waiting list at a methadone maintenance clinic?

I agree that drug abuse is a societal problem and will eventually require solutions beyond what medicine has to offer, but I believe that at the present time, methadone maintenance is a pragmatic solution to a medical problem.

ALFRED E. COODLEY, M.D.
Los Angeles

Free Clinics

To the Editor: I wish to congratulate you on the paper, "Free Clinics in California, 1971" [Calif Med 116:106-111, Apr 1972]. When the survey was first sent out by [Bureau of Research and Planning] the California Medical Association, a great deal of "paranoia" was created in Free Clinics as to your motives for the survey.

Some in organized medicine are opposed to free clinics and I was greatly relieved to see a fair and objective study published.

I might add that Dr. Schwartz's [material on] Free Clinics is published in expanded form in "The Free Clinic: A Community Approach to Health Care and Drug Abuse."

Also I might point out that although some free clinics are in good shape financially (The Haight-Ashbury Free Clinic just received an 8 year NIMH drug abuse treatment grant), others are not. The Long Beach Free Clinic, an excellent program prominently mentioned in the article, is in great need of funds and I hope the Long Beach Medical Society will do more to mobilize community support behind this excellent program.

DAVID E. SMITH, M.D.
San Francisco

In Defense of Corticosteroids

To the Editor: My previous contributions . . . [have had to do with] beliefs and dogmas which although, in my opinion, lacking scientific basis cause no great harm. In this instance I indict a teaching which I believe is causing tragedy for the millions of victims of diseases of hyper-immune mechanism such as asthma, arthritis, colitis and collagen disease. I refer to the emphasis placed on side effects of corticosteroid drugs.

Although moon facing, striae and easy bruising are frequent I am convinced more serious complications are improperly attributed to these drugs. When theory and deductive reasoning are held in abeyance critical appraisal of documented clinical experience indicates that:

1. Steroids *do not* cause *significant* adrenal insufficiency. Despite laboratory evidence of decreased responsiveness of the pituitary adrenal axis, documented cases of deaths attributable to adrenal insufficiency and certainly of adrenal hemorrhage are remarkably rare even when large doses of drugs have been employed. In my own experience, over 600 patients on long term steroid therapy have undergone major surgery without a single instance of adrenal failure.

2. Steroids do not cause peptic ulcer. Palmer and Kirsner[1,2] state, "lesions of the G.I. tract cannot be included in complications of steroid therapy" and "such conclusions are attributable to the *post hoc ergo propter hoc* fallacy."

3. The evidence for significant osteoporosis due to steroids is almost entirely based on extrapolation from Cushing's disease.[3]

My not inconsiderable experience since first employing Meticorten® (prednisone) in 1954 has convinced me that these and other side effects of steroids are more likely attributable to coincidence, too late initiation, too little, and too early discontinuation of treatment.

I have withheld expressing these views for publication because of their controversial nature until reading a news account of a successful malpractice action on the basis of some really novel effects attributed to cortisone. It seems that our chickens have really come home to roost. In this instance we cannot blame the juries or the attorneys but ourselves.

The profession will suffer in increased insurance rates but the real victims will be our patients. A recent article[4] was entitled, "Liability —MD's are Running Scared." If this continues it can well result in abandonment of medicine for homeopathy and naturopathy.

J. J. Robbins, m.d.
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Unwilling Smoking

To the Editor: Soon after the 1964 report of the U.S. Surgeon General on the adverse effects of smoking on health, I began to appeal for a smoke-free indoor environment. I was gratified by the reference in the 1971 report of the Surgeon General to the adverse effects of ambient smoking. In the 1972 report,[1] a section is headed: Public Exposure to Air Pollution from Tobacco Smoke. This section is a powerful answer to critics who allege inconsistency and lack of proper control of statements by the Surgeon General; the presentation not only is a thorough account of available publications, but is notably impartial, and one could never know, from the discussion, which of the quoted articles originated from an agency supported and controlled by German tobacco interests.

The summary of the stated discussion deserves quoting in full.

"1. An atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals.

"2. The level of carbon monoxide attained in experiments using rooms filled with tobacco smoke has been shown to equal, and at times to exceed, the legal limits for maximum air pollution permitted for ambient air quality in several localities and can also exceed the occupational Threshold Limit Value for a normal work period presently in effect for the United States as a whole. The presence of such levels indicates that the effect of exposure to carbon monoxide may on occasion, depending upon the length of exposure, be sufficient to be harmful to the health of an exposed person. This would be particularly significant for people who are already suffering from chronic bronchopulmonary disease and coronary heart disease.

"3. Other components of tobacco smoke, such as particulate matter and the oxides of nitrogen, have been shown in various concentrations to adversely affect animal pulmonary and cardiac structure and function. The extent of the contributions of these substances to illness

> in humans exposed to the concentrations present in an atmosphere contaminated with tobacco smoke is not presently known."

It is apparent that over and above the sheer fact that non-smokers are adversely affected by tobacco smoke, analyses have shown a substantial room-air content of carbon monoxide, nicotine, and carcinogens. To this must be added the important allergenic character of ambient smoke.

Lay-type articles have begun to appear, notably one by John Banzhaf III, (in *Today's Health* for April) representing Action in Smoking and Health. In response to the appeal of this group, HEW has adopted a rule prohibiting smoking in certain contained areas, and segregating smokers from nonsmokers in others. Reference is made also, in the article, to the establishment of no-smoking areas in busses.

I was interested in performing an independent determination of the effect of smoking on the indoor atmosphere. Accordingly, I burned two standard brand unfiltered cigarettes, applying labial suction once each 30 seconds, without inhaling, in a hospital conference room measuring 18 x 30 x 9 feet, having ventilation at 12.5 times per hour. The rate of pollution was considered modest; as many as 12 cigarettes have been observed burning at one time in the stated room. Duplicate samples of air were taken and were examined for carbon monoxide level by Sandra Kerns, under the direction of Hezekiah Moore, of the California State Department of Public Health, Air Industrial Hygiene Laboratory, Berkeley.

The results of analyses were: Preliminary baseline: nil (less than one ppm). At the end of 8 minutes, samples of air obtained at a position corresponding to that occupied by the face of a person seated next to the smoker showed 20.5 and 32.5 ppm. At the far end of the room, 13 and 17 ppm were found. Five minutes after the cigarettes had ceased to burn, CO had fallen to 2 ppm at each position. I concluded from this simple procedure that ambient smoking, over and above resultant symptoms, produces substantial elevation of objectively determined pollutants.

Further, although spatial segregation within a contained area does produce some gradient of pollution, it does not afford proper protection for the non-smoker, even in the presence of effective ventilation; gases diffuse too rapidly for such protection to be attained. Segregation of smokers and non-smokers, to be effective, requires screening by a partitioning structure which will interrupt the movement of air.

Another factor requiring consideration is the physiological or psychological effect of withdrawal in a smoker. Of importance also is the duration of exposure of the non-smoker, as well as the substantial detoxifying effect of inhalation. Should the circumstance arise that smoking within a contained area must occur on an emergency basis, the effect produced in the non-smokers present will be greatly reduced by the performance of a few deep inhalations by the smoker in order to obtain the nicotine effect, which is expectably prompt, followed by prompt extinguishing of the cigarette.

WILLIAM B. DUBLIN, M.D.
Martinez

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Injection Neuropathy

To the Editor: I am writing this note regarding Dr. Barton A. Brown's article on sciatic injection neuropathy, which was published in the May '72 issue of CALIFORNIA MEDICINE. I question the necessity of giving gluteal injections, aiming for a relatively small target of muscle when the anterior lateral thigh is such a vast target for the intramuscular needle. It has been a policy among many pediatric services for a number of years to completely avoid the gluteal injections and thus eliminate the possibility of sciatic injection neuropathy. I should think that our emphasis in teaching people to give injections should be placed on such anterior injections and use of the gluteal area be relegated to a distant alternate if necessary.

I realize, of course, that this goes counter to a good deal of tradition, both in nursing and in medicine, going back many generations. Anatomically, there are not significant vessels and nerve trunks in the anterior compartment of the thigh, whereas the gluteal region, of course, is the site of the sciatic nerve.

JERROD NORMANLY, M.D.
Mountain View

Refer to: Rubsamen DS: No-fault liability for adverse medical results—Is it a reasonable alternative to the present tort system? Calif Med 117:78-93, Jul 1972

Special Article

No-Fault Liability for Adverse Medical Results

Is It a Reasonable Alternative to the Present Tort System?

DAVID S. RUBSAMEN, M.D., LL.B., *Berkeley*

At the request of CMA's Committee on Professional Liability, David S. Rubsamen, M.D., LL. B., has prepared a comprehensive study of the concept of "no-fault" liability for adverse medical results. In what undoubtedly will become a hallmark of further and future consideration of the application of the concept of "no-fault" to medical malpractice, the study concludes that this widely advocated concept is not a viable alternative to the present system of litagating medical malpractice claims. Instead, the study states that: "A no-fault system for compensating injured persons cannot be analyzed outside the context of the injury. . . . In such cases, pursuit of the question leads right back to a standard of care analysis, to conflicts between experts or textbooks or both, to lengthy hearings and even to the accusatory atmosphere—all of which the physician seeks to escape by finding an alternative to customary courtroom litigation."

The report cites, as additional weaknesses of a no-fault system for medical malpractice:

- *Parties in a professional liability action would be denied a jury trial or access to a judicial system based on tort law and its theory of recovery. In effect, physicians would continue to be confronted with accusations, but would lose their ability to respond effectively.*
- *There would be more pressure for defensive medicine.*
- *Rules providing for ease of administration would, because of necessary arbitrariness, virtually guarantee dissatisfaction with the "unjust" result in a significant number of cases.*
- *Patients (perhaps with unrealistic expectations) could easily regard an outcome which is less than they hoped for, as justifying compensation.*
- *Financing of a comprehensive system "would be prohibitive," and administrative problems "could be staggering."*

Dexter T. Ball, M.D., Chairman
CMA Committee on Professional Liability

NO ONE DOUBTS THAT THE TORT-COURT TRIAL system for professional liability cases contains profound defects. A steadily rising incidence of claims, the irrationality of 12 lay persons attempting to resolve frequently complex medical issues, the years of never-quite-absent anxiety if he has a case pending, plus the particularly distressing prospect of public trial and probably excoriating cross examination (all to be repeated if a new trial is granted by an appellate court) create a picture of torment for the sensitive phy-

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The author is a medical-legal consultant and chairman of the CMA Liaison Committee to State Bar of California and a member of the CMA Committee on Professional Liability.

This report was transmitted by the CMA Committee on Professional Liability which recommended its publication in CALIFORNIA MEDICINE.

Reprint requests to: Mr. J. E. Curley, Jr., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

sician and at least of wasted time and unpleasant incidents even for the more resilient. The current claims frequency,[1] unless it drops considerably, makes the litigation experience a likely prospect for every California physician at some time in his career. And the whole problem is compounded by an instability in insurance rates which presages substantial yearly increases in premiums for at least that group of California physicians whose claims experience in recent years excludes them from the "preferred risk" classification.[2,3]

For the patient, the tort-courtroom litigation system is unsatisfactory. Leading plaintiff's attorneys in metropolitan centers allege that they turn away at least 90 percent of persons who feel they may have been negligently injured by a physician or a hospital employee. Some of these patients have valid claims which are too small to justify the necessary investment of the lawyer's time. Although among the remainder of cases a number must be essentially frivolous, it is logical to suppose there is a significant group of patients with substantial disabilities which are medically caused but do not seem associated with negligent care. And it is generally felt that patients who sue physicians in the more rural counties must have far stronger cases in order to win. Taken together, then, there is a significant group of uncompensated injuries which, although frequently not the fault of the physician in a legal sense, constitute for the patient a dismaying and perhaps expensive consequence of his medical care.

Even for the patient who is destined to win in court, the road is not free of obstacles. In San Francisco and Los Angeles there will be a substantial delay before trial. If the patient is successful, but the verdict is appealed, there will be additional delay.

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[1] Fourteen per 100 physicians in Northern California and probably not far behind that in Southern California, although recent data from that area are incomplete.

[2] Professional Liability Newsletter, Vol. III, No. 8 for October, 1971, describes the underwriting policies of California's professional liability carriers and analyzes the potential instability in this state's insurance market which may result from these underwriting policies. Although obviously conjectural, it is likely that physicians in the particularly vulnerable specialties (neurosurgery, orthopedics, anesthesia, etc.) who do not find themselves in a preferred risk classification will be faced in six or seven years with premiums of $10,000 for adequate liability coverage. American Mutual Liability Insurance Company, the one California carrier which neither seeks the preferred risk physician exclusively nor rates up certain of the insured within its group program, anticipates an increase in premium for all classifications in 1972. Will this drive many of their preferred risks to carriers who seek such physicians and will write them at a large saving? Will attrition in this preferred risk segment of their insured mix worsen the company's loss ratio, thus producing even higher premiums? The possibility of a vicious circle is obvious. As a rough estimate, perhaps one-quarter to one-third of California physicians covered by private carriers fail one common test for preferred risk status—that is, no loss (either settlement or verdict) in the last five years and no current open file against them. Over the next four years will the carriers who seek the preferred risk physician be able to maintain their rates, while the group carriers progressively raise theirs? Will groups, such as Hartford and CNA, which rate up some of their insured, be able to maintain favorable loss ratios by that means? Given the worst prognosis for the group carriers, extinction after a few more years, California physicians would find themselves in two classes: preferred risks who could obtain coverage at relatively reasonable rates and substandard risks insured at very high rates. It is the possibility of such changes which creates a feeling of urgency among those looking for alternatives to the current system of litigation.

[3] Instability in the professional liability market is created by a variety of uncertainties. For example, will judicial decisions over the next ten years further increase the doctor-defendant's risk of liability? In one area alone, that of informed consent, a single innovation (eliminating the need for an expert witness to establish the defendant's failure to warn adequately of risks incident to treatment) might sharply increase losses and certainly would increase the amount of litigation. Probably the most important uncertainty relates to the long "tail" on losses assigned to any particular year. Thus, in October 1970 a San Francisco jury awarded $500,000 for an anesthesia accident which occurred in May 1959. Because the patient was only 13 years old at the time, he had eight years plus the statutory period in which he could file suit. Assume that a company suffering such a loss had collected $2,000,000 in premiums in 1959. It is easy to see that what might have been a slightly favorable loss ratio for that year could be turned into an extremely unfavorable one. Is there an accelerating incidence of high losses such that even the high premiums in 1971 may not cover those losses attributable to this year which accumulate over the next 20 years or so? In the first three months of 1971 there was a $650,000 verdict in Los Angeles, $670,000 and $600,000 verdicts in Northern California and a $200,000 settlement in Northern California. These last three losses were against a single company. Early 1971 was also noteworthy for a 1.9 million dollar verdict against a Southern California manufacturer of intravenous solutions. The remainder of the year saw half a dozen verdicts in the range of one-half million dollars and a 2.7 million dollar verdict in Los Angeles against a drug manufacturer. These two drug manufacturer cases are mentioned only to illustrate what juries can do, given the appropriate facts; each of these two cases involved a single injured person. More importantly, these very high verdicts in the professional liability cases simply were not anticipated as recently as five or six years ago. Some actuaries have questioned whether standard methods are adequate to predict future losses in the professional liability field, given the variety of unstable factors affecting losses.

These are only the direct implications of the current system for the patient. Equally important, but more subtle, are the consequences of treatment made more expensive by "defensive" medical practices, such as laboratory evaluations and x-ray studies which are mainly designed to present a good record in case a suit should materialize.[4] The transferred cost of liability insurance from physician to patient makes care more expensive and promises to be of greater significance in the future. Finally, what can be said in defense of a system which, at least for some physicians who have suffered through litigation, places the patient in the position of being a potential enemy? How often does the patient, seeking only an honest explanation from his physician for an unexpected complication, find himself treated coolly, given little or no explanation, and left with the feeling that the physician's anxiety about a possible law suit takes precedence over his concern about handling the complication?[5]

For the social theorist, the current system presents a defect which he regards as more serious than those noted above. He sees the tort system as inadequate in terms of "outcomes measurement" and thus ineffective in promoting changes which are necessary to reduce medical injuries. That is, of the total number of medical injuries which occur, only a small proportion are actually litigated. Hence adequate data about injuries are not available to those who might promote medical improvement and reform, ultimately to the benefit of all patients. There are only a few papers which put forth the views of these theorists, but it seems they regard medicine as poorly motivated to accomplish adequate internal policing and look to leadership on this point from forces outside medicine.[6]

What about solutions? Parallel to more direct action, reflected in several pieces of legislation sponsored by the California Medical Association,[7] there has been a continuing effort at state and local levels to upgrade practice, especially within hospitals. Neither effort is a definitive solution: On the one hand, regardless of the efficiency of postgraduate education, it is realistic to anticipate a certain irreducible incidence of negligent injuries as well as an additional incidence of medical complications which will lead to adverse verdicts even though there has been no substandard care. On the other hand, although legislation to date has been helpful, it is generally agreed that the medical profession cannot anticipate the sort of sweeping legislative change which would present a serious impediment to the plaintiff's pursuit of a given claim, especially where it is a valid one. Thus, in recent years informed physicians have directed their attention to substantial changes in the tort-courtroom system itself.

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[4] Of course, not all defensive medicine is bad. The physician who seeks consultation because he wants to protect himself in case of a bad outcome may be doing the patient a critical service when the consultant identifies some vital but overlooked facet of the patient's disease. Overuse of chloramphenicol unquestionably has been sharply reduced as the result of several well publicized law suits. The risk of liability for hospitals probably accounts, at least in part, for the variety of rules which benefits patients by imposing peer review, tighter procedures, and the like.

[5] Leonard D. Fenniger, M.D., former Professor of Surgery at the University of Rochester and currently Associate Director for Health Manpower at the National Institutes of Health, recently stated, "When the New York Times Sunday Magazine Section devotes seven or eight pages to an article by a physician in Washington describing the changes that have taken place and how he deals with the problem of the people who come to him for help and how much more defensive he has gotten over the last five years because of rising liability—when the New York Times devotes that much space to that kind of problem, I think it is fairly evident that it is much on everyone's mind. Ultimately, the present trends in medical liability actions will affect the choice of careers by individuals who may wish to go into medicine or into one of the health professions or one of the health occupations, but who decide that the risk is simply too great and, therefore, choose something that has less apparent risk. There will obviously be increasing effects on the availability of services and the choice of the services that are given to people who need them. In other words it may result in elimination of high risk but also highly therapeutic technologies simply because the risk and the threat are greater to the person continuing the practice of his profession than the gain that might be received by the patient through the use of a particular technique or a particular therapeutic regimen which has a fairly high inherent risk." And later in the same speech Dr. Fenniger said, "The increasing litigation, the rising cost associated with it, tend to produce an increasing number of elements that have absolutely nothing to do with the judgment based on medical knowledge or the well being of the person who is being served. I trust that there will be discussion on how one can go about making early settlements of differences. This is absolutely essential, not only from a dollar cost point of view, but particularly from an emotional and social point of view, because if one watches the devastation of a human being in a family while a case is in court for three or four years, the social cost is absolutely enormous and cannot be measured by any yardstick of dollars. We are all involved—we are all responsible in the last analysis. The decisions are going to be social and political, as well at medical and legal. Our best and generous advice is essential if the political decisions are going to the wise ones."

[6] It is frequently stated that federally sponsored health insurance will be a prime stimulus for more concern with quality control of medicine. There is an assumption that once a society satisfies its need for health care in a quantitative sense there is then an inevitable shift to concern for quality of care.

[7] A more restrictive statute of limitations, insulation of the minutes and records of medical review committees from discovery, the right to bifurcate a professional liability case so that the issue of the statute of limitations may be tried first, authority on the part of insurance companies to make advance payments to an injured patient without such an act being construed as an admission of liability, and immunity from liability for cardio-pulmonary rescue teams are all significant legislative achievements. A cost bond law and immunity from liability for the physician who in good faith takes over a case from another physician when a complication arises are statutes written in a manner as to make their value questionable.

One change, which retains the tort system but eliminates the courtroom proceedings, is binding arbitration. California leads the nation in developing experience with this device. A substantial number of cases can be anticipated from Southern California-Kaiser which a year ago began requiring arbitration contracts with all of its members (more than 900,000).

Payment for adverse medical results without regard to fault (no-fault) eliminates the tort system altogether. This is the subject of this paper.

Payment for injury, regardless of the amount of care which was exercised by the defendant, is nothing new in Anglo-Saxon law. Although the question is disputed, a noted scholar, referring to English jurisprudence in the early 12th century, states, "The doer of a deed was responsible whether he acted innocently or inadvertently, because he was the doer. . . ."[8] and even 100 years later books which recorded the pleadings in the Royal Court revealed nothing resembling a negligence action.[9] The concept of due care seems implicit in a number of cases that were tried over the next 200 years, but it was not until the early 1500's that the Chief Justice of the King's Bench said, "It is the duty of every artificer to exercise his art rightly and truly as he ought." Subsequently this duty of care is referred to frequently in cases involving innkeepers and common carriers who lost customers' goods. But it was not until 1792 that an annual compilation of Royal cases offered an incidental heading which mentioned "negligence," and it was 1843 before negligence was treated as an isolated subject in an authoritative compilation of cases heard in the Royal Court.

The restrictions placed on the plaintiff's right of recovery in a negligence action were formidable in the 19th and early 20th centuries, and are usually attributed to a concern for unfettered development of burgeoning industry. Reversal of this trend began after World War I and has accelerated during the past 15 years. The rule of strict liability as applied to latent defects in manufactured products is an excellent example: The negligently manufactured product which causes injury will, of course, create liability for the manufacturer. But what about the defect in a product which is not discoverable in the course of careful manufacturing and inspection procedures? In a pioneering California case in 1963 the California Supreme Court ruled that, as a matter of social policy, the manufacturer should be required to pay. It was reasoned that if he could anticipate strict liability for injuries resulting from every defective product it would be a simple matter for the manufacturer to insure himself, whereas the injured party would generally be less well equipped to face financial losses. A similar rule of strict liability has been applied to food products for many years. The Pennsylvania and Illinois Supreme Courts extended the rule a year ago to include virus-contaminated blood. Recalling the degree of insulation from legal liability which the manufacturer and food producer enjoyed at the turn of the century, their present status implies an almost revolutionary change. And this change has occurred through judicial decisions rather than legislative fiat. The current trend in no-fault liability for auto incurred injuries reflects a similar concern for the welfare of injured persons, one which is codified by legislation.

It is in the context of this gathering wave of "consumerism" that one can best view the professional liability picture in California over the past 20 years or so. Our courts have frankly stated their intention to equal the balance between the patient who sues and the physician who defends by progressive expansion of the evidentiary rule of *res ipsa loquitur*. Juries, at least in metropolitan areas, also seem far more concerned than they were a number of years ago with the plaintiff's plight as compared with the physician's. Unquestionably there are additional factors (large contingent fees, the increasing skill of the plaintiff's bar, the public's increased awareness and acceptance of litigation), but most writers on the subject regard the physician's professional liability problem as fundamentally similar to that of others who provide a product or service for a fee—all share an increased risk of legal liability as compared with even 10 or 15 years ago.[10] In this context the physician's risk of professional liability can be seen as something other than an aberrancy; it is not an angry public "taking it out" on physicians. It makes sense, then, to assume that the peak of our liability problem is far ahead, and it is timely to look for some fundamental solutions.

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[8] Wigmore, Selected Essays in Anglo-American Legal History (1894) p. 480.

[9] Percy Winfield, History of Negligence in Torts, Law Quarterly Review. Vol. 42, p. 184 (1926).

Is no-fault liability for adverse medical results a viable solution? That is the question. Philosophical discussions on the point are interesting but defy accurate analysis because they depend so much on opinion. Besides, there is a basic issue which must be addressed first. Will it work?

This initial question takes precedence over the problem of financing a truly comprehensive no-fault system, although that would require premiums far in excess of those the medical community can foreseeably afford. And it is only indirectly concerned with administrative problems which, depending on the type of no-fault system adopted, could be staggering. Rather, the question is addressed to the most central issue in any compensation scheme, whether based on a fault or a no-fault system. That is, how does one identify the compensable events?

For some medical injuries it would not be difficult to establish causation in a no-fault scheme. Vesico-vaginal fistula following hysterectomy, for example, is a consequence of the operation. That is, but for the operation it would not have occurred. The surgeon's explanation that this can occur absent negligence carries no weight, because payment for the injury is made regardless of any question of fault. Virtually automatic payment in such a situation might be welcomed by the physician if it is alternative to a lengthy lawsuit, a two-week trial, possibly appeal, a possible re-trial, and so on. For the patient, there is an immediate financial recovery which, although probably smaller than a settlement or a jury verdict which might eventuate (and, on the average, the chances for a plaintiff's verdict with this particular type of injury would not be very good), is at least certain. And the money is available almost immediately, rather than a few years hence. The social theorist is satisfied because immediate payment for vesico-vaginal fistulas will soon supply his office with data concerning which physicians and hospitals seem vulnerable to this accident, and he can take action to remedy the situation. It is this sort of example, relatively clearcut injury after an easily defined medical intervention, on which theorists focus when they write about no-fault liability. But what about all of the other medical incidents (complications and injuries) which, but for medical treatment, would not have occurred? As discussed next, an evaluation which focuses on the cause of a particular untoward result of treatment, in order to decide if compensation is deserved, introduces complexities into a no-fault system which must strangle it.

Recognizing this defect in a no-fault system which is oriented toward analysis of treatment process, one research group in this field[11] has directed its efforts toward developing a "technology of treatment outcomes." This result-oriented approach is still in the conceptual stage, but it raises a number of important questions.

There are solutions which can be characterized as "partial no-fault" systems. One or another of these may have some real appeal, perhaps mainly because of their comparative administrative simplicity.

Compensable Events

A Literal No-Fault System

Taken literally, a no-fault system of compensation for medical "injuries" means payment for every unanticipated disability which, but for the medical intervention, would not have occurred. Albert Ehrenzweig, a professor of law at University of California, Berkeley, apparently advocated this literal rule as early as 1964 in a University of Chicago Law Review article.[12] Limiting his consideration to the hospitalized patient, Professor Ehrenzweig cited a study which placed the incidence of "hospital accidents" at 3.4 percent of all patients admitted. He says, "This insurance would enable the patient injured by a 'hospital accident,' i.e. *a failure in the process of his treatment* relating to services which were rendered or should have been rendered . . . . to claim the benefits of the policy without having to identify any specific injurer or a causative 'negligence' . . . ." And, "The patient would be assured a minimum recovery for any *injury to his health* that he might sustain for reasons other than those *induced by his illness* during his stay at the hospital." (Emphasis added.) In a recent, unpublished paper Professor Ehrenzweig's approach to the compensable event is the same.

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[10] For the past four years the Inter-professional Committee of the San Francisco Medical Society has met with engineers, architects, attorneys, and other professionals in order to discuss a variety of topics within our common interest. With regard to their professional liability each has described concern. Construction engineers, and especially architects, currently have liability problems which, for some specialties within these fields, are greater than those faced by physicians.

[11] The Institute of Interdisciplinary Studies, Minneapolis, Minnesota.

Only a few illustrations are necessary to describe the scope of the problem (and it is undoubtedly greater than foreseen by Professor Ehrenzweig) raised by a literal no-fault rule. Shall every disease process which pursues its inevitable course to serious disability, or every death after coronary occlusion, after overwhelming bacterial or virus infection, after head injury, after hemorrhagic shock, and the like, provide survivors with a right of recovery only providing it can be shown that there was some omission, some alternative judgment, some more suitable intervention which would, in retrospect, more probably than not have saved the patient? These problems of judgment and omission (as opposed to the analysis of some specific intervention) bear special emphasis.

What of the physician who decides not to take an electrocardiogram when the patient presents to him with minor chest pains? When the patient dies of a myocardial infarction at home, a few hours later, it is the physician's erroneous judgment and his omission which account for the death. (Recall, we are speaking here of no-fault liability.) "Erroneous" in this context does not refer to carelessness, but only to a straightforward fact—but for the failure to identify the infarction with an EKG (assuming that the tracing would have been diagnostic at this early stage) the patient could have been admitted to a hospital and his life probably saved. Thus, because we are talking about a literal no-fault rule (being only concerned with causation) the issue of negligence simply doesn't arise.

And what of the patient with early gastric cancer who presents with mild indigestion, the bowel malignancy with only modest lower abdominal complaints, or the brain tumor with only a rather persistent but not severe headache? The physician's defense against a charge of *negligent* failure to diagnose a gastric cancer, a cancer of the lower intestinal tract, or a brain tumor will emphasize the reasonableness of any delay in performing an upper gastrointestinal series, proctoscopy and barium enema, or skull films and electroencephalograms. But again, a literal no-fault liability rule looks only to causation. If the patient with the indigestion has a gastric cancer and the physician waits before taking films, the only question which the patient, or his widow, seeking benefits need pose is whether or not the delay prevented cure.[13] So also with the lower intestinal cancer or the brain tumor.

Any physician can think of numerous similar examples. Two consequences of a literal no-fault system as it applies to judgments or omissions and a variety of interventions will be: First, a flood of administrative proceedings (probably on the order of industrial accident hearings) to determine whether or not the patient or his heirs have a right to benefits, and second, a pressure for defensive medicine far in excess of anything present today. It is clear how these two feed on one another—even though there is no onus of fault, the physician will want to avoid these administrative proceedings. They would take up a good deal of time, and for many physicians the nature of their practice would place them in these hearings several times a year. So even if there were no adverse consequences of repeated findings against the physician, it is inevitable that he would rapidly come to the conclusion that only a perfect set of records could constitute a reasonable "defense" in these cases.

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[12] "Compulsory 'Hospital Accident' Insurance, a Needed First Step Toward the Displacement of Liability for 'Medical Malpractice'." University of Chicago Law Review, Vol 31, page 279 (1964).

[13] Obviously, even the most literal no-fault system would require *some standard* for evaluation of the physician's conduct. For example, how persistent would the gastric symptoms have to be in order to create suspicion? But create suspicion for whom? The *most alert* physician? This would be the extreme test. The absurdities growing out of a literal no-fault system are analysed further, below.

A literal no-fault system, as applied to the above cases, only requires establishing medical causation. But there is another group of cases where proving medical causation is just the first step in determining if the disability shall be compensable.

In these cases medical intervention is associated with a well defined, and not small, incidence of disability. Thus, chemical management of cancer is associated with an inevitable incidence of toxic reactions to the chemical. Aggressive as opposed to conservative management of a given case may carry a better ultimate prognosis for the patient, yet the aggressive treatment may carry with it a high risk of immediate and dramatic disability or death. In these examples, while it is true that but for the medical management the complication would not have occurred, the inevitability of complications makes automatic compensation seem unjust. And, far more importantly, to the extent the physician sees compensation as somehow a penalty against him, he will be reluctant to undertake medical management which carries with it the risk of these inevitable complications. Therefore, it probably would be administrative policy to deny compensation for those medically caused disabilities which were not only recognized risks of the treatment given, but, in the particular case at hand, truly unpreventable.

But how does one separate the preventable from unpreventable injury within this calculated risk group?[14] This can only be done by scrutinizing all aspects of the treatment process (the physician's judgment, the presence of any omission, and similar factors, and their relationship to the ultimate disability). Isn't it immediately apparent that this requires a standard of care analysis? Not in negligence terms, deciding what is "ordinary care" and then testing the physician's conduct against that standard, but in the frame of reference of actual causation. That is, was every aspect of his management, every facet of his judgment, so excellent that it is reasonable to conclude the complication was unpreventable? Alternatively, perhaps the physician could identify the particular disease mechanism which produced the complication and then demonstrate that neither could he have prevented that particular mechanism nor did he by his management promote it.

When Professor Ehrenzweig and other legal writers refer to medical injuries, they seem to select as their point of reference some specific intervention, usually surgical, which produces a reasonably obvious bad result. Yet, as I have indicated above, Professor Ehrenzweig would compensate any injury to the patient's "health that he might incur for reasons other than those induced by his illness during his stay in the hospital." Would it make sense to compensate only injuries resulting from *interventions*, excluding those resulting from errors in *judgment?* Of course not. This rule would reward the temporizing physicians in situations where delay could be unwise or even negligent.

Note especially that a literal no-fault rule requires that the administrative officer simply ask if a judgment was correct, not if it was wise. Thus, a physician who left his patient with acute myocardial infarction in a hospital which did not have a coronary care unit might be equally liable, if he guessed wrong, compared with the physician who transferred such a patient to a hospital which had a coronary care unit but the patient died on the way. If the administrative officer decided there was causation—that is, that moving the one patient caused his death or leaving the other in the hospital without the coronary care unit caused death—then compensation would have to result.

> *Comment:* Is it not a virtual caricature to identify a no-fault system with such an impossible burden for the physician? A burden which, despite the elimination of an accusatory atmosphere, still must be very onerous as he finds himself in hearing after hearing, trying to explain every detail of his conduct. Therefore, if a literal no-fault system were introduced, it seems apparent that a standard of care which required perfection in medical management would be absurd. Similarly, the "but for" test which is implicit in a literal no-fault system, as referred to in my first group of cases above, would be far too strict. What

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[14] A certain proportion of complications which are "within the risk" of a procedure would not have occurred if excellent judgment or technique or both were applied. And in a smaller proportion of cases injuries would not have occurred if ordinary care had been used. In other words, to say that a given disability is a calculated risk of a particular procedure does not mean it was literally unpreventable; it is only a statistical assertion which, in the defense of a professional liability case, is the first step in seeking to show that in the particular case at hand the complication was indeed unpreventable.

standard of care shall be required then? Excellent management? Very good management? An ordinary care standard would simply reintroduce the negligence system in a different form; so it would no longer be a no-fault system. But the necessity for introducing and then manipulating a standard of care in a literal no-fault system underlines its central defect: It is still an essentially accusatory system under another guise, one which may largely remove the opprobrium of a claim, but at the same time multiplies the number of claims many fold. The forum is shifted from the courtroom, but the requirement for detailed analysis of medical facts is not lessened.[15] Picture the conflict between experts, or expert and textbook, as the hearing officer seeks to determine the best standard of practice in a given situation!

Another common issue to be decided by the hearing officer at an administrative proceeding would be whether the particular judgment, omission or intervention, even if it were below the particular standard of care being applied, produced the disability of which the patient complained. This is similar to the familiar causation issue in negligence cases. Example: Granted that the doctor-defendant failed to identify a pulmonary carcinoma when the first definite signs appeared, if it can be proved that there were already metastases at that time, then his dereliction had nothing to do with the patient's death.[16]

And how would the administrative officer, in a no-fault proceeding, handle contributory negligence? Assume the patient is carefully instructed to notify his physician about a change in symptoms, and then does not do so. This could be treated as contributory negligence in a tort action, thus barring recovery. In no-fault auto injury schemes and Workmen's Compensation, contributory negligence is not a bar to recovery, although self-inflicted injury is. If a patient carelessly takes excessive amounts of a drug, injuring himself, is that a self-inflicted injury or contributory negligence?

Finally, regardless of the standard of care which the administrative agency applies, shall it be the same for the remote rural practitioner as for the metropolitan specialist? Again, because we are dealing with no-fault, the question of fairness (theoretically at least) does not arise. Thus, the protection which the rural practitioner receives from a sympathetic local jury or from legal rules which do not apply a specialist standard in evaluating his medical management (assuming that he was in a situation where no specialist was either indicated or could be obtained) would not be justified.

Compensation Based on "Comparative Casuality"

At a recent conference in Santa Barbara[17] J. W. Bush, M.D., presented a mathematical model designed to compensate patients for injuries traceable to "non-standard" medical management. The model seeks to establish a "coefficient of causality." This is derived in the following manner: Assume a patient suffered a fractured cervical vertebra incident to a fall. He was treated by traction with Crutchfield tongs, but treatment was unsuccessful and the net result was quadriplegia. Assume further that there is expert testimony that prognosis in this type of case would be slightly improved if the patient had been treated early with surgical decompression of the cervical spine. And, finally, assume that expert testimony establishes that there was only a 1 percent chance of recovery with traction alone but a 4 percent chance with the surgical procedure. The patient, then, was denied a 3 percent chance of recovery through failure to accomplish operation. In this example Dr. Bush regarded the total value of the disability as

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[15] The no-fault rule for auto injuries is easily applied because it is easy to focus on the crash. Did the patient have a significant disability before that event? Is the alleged disability residual from the accident only a continuation of that which existed before? Only occasionally will these questions be especially complex, and even then the accidental event gives them a precise frame of reference. Similarly with no-fault liability as applied to industrial accidents. The great majority of time there is a particular accidental injury injury affecting a previously healthy individual. It is common to find lay commentators on no-fault liability for medical injuries treating the compensable event issue as differing only in degree from these examples. But it is apparent from the foregoing that there is a vital, qualitative difference: particularly in the area of judgments and omissions, the already ill patient who presents himself to the physician or hospital may have his illness prolonged, ultimate disability made more severe, a new disability (illness) introduced, etc., depending on what the physician does or fails to do.

[16] Since negligence requires not only a failure in due care, but a nexus between this and the ultimate injury, the physician would not be liable.

[17] "Medical Malpractice, a Discussion of Alternative Compensations in a Quality System," the Center for Democratic Institutions, Santa Barbara, California, September 1971.

$250,000. He identified the "coefficient of causality" as 3 percent (the difference between the 1 percent chance for recovery with traction and the 4 percent chance with operation) and 3 percent of the $250,000 gives a figure of $7,500. That is the patient's award for his quadriplegia.

Dr. Bush states, "The net effect in the long run is that all patients who are injured—under circumstances in which unacceptable medical treatment contributed to the proximate cause—would be awarded something, and the award would add up to the total amount of disability imposed upon the population by health care providers." He envisions authoritative medical panels, composed of physicians in the various specialties, making these determinations. He concludes that this system would readily identify the incidence of poor treatment results in a given community and that it has a particular advantage in assimilating "proven innovations in health care which would affect the determination of what is standard or non-standard" medical practice.

> *Comment:* This system offers no relief from a detailed analysis of the medical treatment process imposed by a literal no-fault system. Additionally, the "comparative causality" concept fits into a fault rather than a no-fault frame of reference. Dr. Bush frankly states this fact. Yet the assignment of fault is associated with a very high standard of care (*i.e.*, would another treatment, another judgment, etc., have produced a better result?). This runs counter to the traditional feeling that retrospective assignment of blame, applying such a high standard, is unjust.[18]

A Result Oriented No-Fault System

R. J. Carlson, a research attorney at the Institute for Interdisciplinary Studies in Minneapolis, presented a concept at the Santa Barbara Conference which seeks to finesse causation issues altogether. It is Mr. Carlson's premise that "compensation for medical injuries should be tied to the degree of deviation of a given result from a set of expected results for like procedures." That is to say, "If the health care industry is conceived as an enterprise occasioning compensation for those who suffer harm through the conduct of that enterprise, a determination must be made whether or not the patient's prognosis at discharge (or at the time of filing a claim) is 'worse' than it should have been, or 'worse' than expected, *given* the procedures and regimen of care utilized for that patient. This is required unless a social insurance system unique to health care is created which would compensate any state of disability occasioned by health care even if the result of care was wholly expected. For example, a gangrenous leg must be removed; if it is removed, the patient has one less leg and would therefore be compensated for that loss."

> *Comment:* The implications of a social insurance system for medical disabilities is considered under a separate heading below.

For physicians this concept seems peculiar, because our orientation is toward accurate evaluation of medical events. So a reparations systems which is inefficient in identifying the individuals to be compensated seems both clumsy and unjust. But the "social engineering" implicit in Mr. Carlson's concept is not focused primarily on justice for the injured individual, rather it is designed to improve the health care system. Thus, it is envisioned that compensation for unfavorable outcomes of medical treatment would bring to the attention of the administering agency (and this could be medical or public or a combination of both) a very large number of cases. It is postulated that additional analysis of these cases would be undertaken, not to clarify further the accuracy of the decision to award a given patient, but to evaluate the competency of the medical care. Then data accumulated about quality of care would serve to bring pressures, of a nature undescribed by Mr. Carlson, on the "health providers," whether physician, hospital, or other, to the end that effectiveness of services might be improved.[19]

Does this "outcomes analysis" only look to results as a basis for compensation? This is not literally true, because it is a deviation from expected results which rings the compensation bell. So it is inevitable that the prognosis in a given case be based on something more refined than an admitting diagnosis. Therefore, some additional data about the patient's presenting condition will go into the equation, but this will fall far short of the detailed evaluation necessary to establish medical causation. As Mr. Carlson stated in his Santa Barbara presentation: "A no-fault system strips away the interrogative aspects of malpractice and focuses instead on the nature and extent of a patient's prognosis. The physician is no longer made the subject of an extensive examination in order to determine whether any recompense will be made; nor is the concern, for the purposes of compensation, with discrete provider behavior in an episode of care."

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[18] It was suggested at the Conference that Dr. Bush's comparative causality analysis might have its best aplication to rare medical or surgical accidents which are a calculated risk of a given treatment or procedure. Thus, if vesico-vaginal fistula is preventable by excellent surgical technique and judgment 85 percent of the time, but is unpreventable 15 percent of the time, then a standard award for this disability could be reduced by 15 percent.

[19] Mr. Carlson puts it this way: "While assessments of compensation are made without references to the behavior of the providers, once compensation issues have been resolved 'process reviews' of provider behavior (and other 'disciplinary' mechanisms) to correct sub-performance ostensibly contributing to (if not proximately causing) the claim in question can and should be made."

Obviously the next question is, Who shall decide when there has been a "deviation from expected results?" Speaking in Chicago in March of last year,[20] Mr. Carlson noted: "A compensation system for medical injury not based on fault would require the development of norms or scales of health care outcome. This is an enormously difficult scale to develop, and I would like to add, parenthetically, that the resource organization with which I am working and particularly a research project with which I am involved is looking at a no-fault compensation system for medical injuries. We have been looking at it for eight months and I suspect we will be looking at it for a lot longer than that. The toughest question of all to deal with in medical care is that of a technology available to develop scales of outcome. We haven't resolved this question, although we have contacted, talked with and have had conferences with, the leading experts in the country on the question of outcomes for health care. We think we are breaking some ground. We think we will be able to develop some tentative scales for health care outcomes."

When Mr. Carlson talks about departure from an anticipated result, his usual frame of reference seems to be a case where there is some specific intervention, most often in a hospital environment. But what of this analytical approach in more subtle situations, for example the failure to make a diagnosis in an office practice? Take the patient who is seen by her physician every few months and develops a breast cancer during this time. Or what of the patient who presents with a mild febrile illness which is treated with aspirin, then goes home and develops a fatal meningitis? What if the fever was low grade, the sore throat mild and these occurred when a number of patients in the community were manifesting epidemic virus respiratory infections? Were the patient's parents carefully instructed to contact the physician within 24 hours and did they then not do so? Is it reasonable to suppose that the meningitis wasn't present at all when the patient was first seen, developing only later from the upper respiratory infection? It is one thing to talk about a "deviation from expected results" where there has been surgical operation, but how can one talk about the "expected results" in this meningitis case without analyzing every facet of the presenting problem and subsequent course? Similarly with the breast cancer example. How often was the patient seen, how often were the breasts examined, what were the notations in the medical record, and what was the location of the cancer once it was identified? Was there metastasis by that time?

In cases involving less than optimal judgment, and assuming that this accounts for disability, what does the "technology of outcomes" do for us? Assume there is a mistaken diagnosis. Can this technology simply look at the number of days before the full blown, recognizable disease that the patient was seen and then draw conclusions concerning the presumed adequacy of the physician's diagnostic guess? Every time he guesses wrong, and the patient suffers because of the delay in accurate diagnosis, shall there be compensation? More importantly, how does the outcomes approach handle an allegedly substandard judgment in the course of a highly complex disease process?

For example, a physician makes one or more judgments in the course of treating a patient with severe diabetic acidosis. For the sake of argument, assume that at least one of these judgments was clearly negligent and caused the patient's death. Can a system of compensation avoid being capricious without a careful analysis of treatment process in cases of this type? This leads right back to the complexities and absurdities of a literal no-fault system.

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[20] "A Conference on Liability for Medical Injuries" sponsored by the Comprehensive State Health Planning Agency, State of Illinois, March 1971.

Perhaps the advocate of outcomes analysis would argue that death following uncomplicated diabetic acidosis will be considered a deviation from an expected result. This finesses the treatment analysis. But what if the patient in my illustration entered the hospital with a variety of complications? Perhaps he was in shock, had early heart failure and auricular flutter. Is this a case in which, should the patient die, there should not be compensation? Now assume that each of these complications was swiftly and effectively treated by the intern or resident staff, the errors being effected later on by the patient's private physician? How can the case be shifted back to the compensable category without an analysis of the treatment process?

More commonly, there is the uncomplicated illness which becomes complicated, and unpreventably so, during treatment. If there is residual disability, shall there be compensation just because the initial diagnosis implied a favorable outcome? And if the physician is permitted to "defend" by putting the complication in "evidence," the patient must be allowed to rebut by arguing it was preventable. So the standard of care issue must be analyzed through expert testimony, or textbooks or both, and the parties again face the same problem as in a literal no-fault system.

To the extent that less than satisfactory results of treatment are characterized as deviations from expected results (and keeping in mind that this system does not include significant analysis of the treatment process) many physicians will regard this approach to no-fault liability as capricious. In view of Mr. Carlson's suggestions (considered below) about regulation of physicians based on data concerning medical injuries, it is inevitable that physicians would come to regard the system as accusatory. In a variety of areas, therefore, and especially with regard to diagnostic judgment (does this patient need an EKG for a mild chest pain, does this baby require treatment in hospital for what seems to be self-limited diarrhea, should this patient with nonspecific gastrointestinal complaints have an x-ray study), there is the likelihood of defensive medicine with a vengeance.

> *Comment:* It is important to note that Mr. Carlson regards the "technology of outcomes analysis" as undeveloped at the present time. In a recent conversation he told me that his scheme is only a "social and conceptual approach to a problem" and does not pretend to be a solution which has been filtered through a large number of evaluations by clinicians in order to test all facets of its applicability or acceptability to the medical profession. However, his project is important because it represents the most intensive study of this particular no-fault approach, and it is on-going. It is planned that Utah will run an experimental program, purely on paper, without any implication for payment to patients or discipline of physicians. The current interest in no-fault in the country is illustrated by the appearance already of a bill in one of the smaller state legislatures, proposing no-fault liability in malpractice cases.

At Santa Barbara Mr. Carlson made these observations about the implications of "provider self regulators" associated with his plan: "There have been two reasons for the failure of much provider self regulation thus far. The first is that regulatory systems have been and are controlled by providers, violating a fundamental precept of regulatory theory. Paradoxically, however, the capture of the disciplinary process has not been covert but designed by state enabling legislation, mandating provider controls of the disciplinary machinery. The second reason is that, while competence is acknowledged to be important by providers, lacking definitive measures of competent performance, disciplinary proceedings have not been based on such grounds. This in part is because providers have been able to argue that to do so will be both unfair and capricious. Of course, state laws with rare exceptions have not recited 'competence' as a ground for disciplinary action, but such statutes are virtually dictated by organized medicine in most states and thus only mirror the prevailing sentiments of providers on the question. A shift to no-fault compensation should, however, increase the likelihood that disciplinary statutes will reflect a concern for competent performance; utilize such indisputable evidence of provider's subperformance as is available through recorded process reviews of provider behavior occasioning claims; and finally relax the grip of providers over regulatory agencies by lessening their concern over consumer involvement because the judgment to be made in disciplinary cases are less subjective and presume less expertise under no-fault. All of this can be reasonably expected because a no-fault system is ostensibly more compatible with the professionals' view of the appropriate means to assess competence and penalize incompetence."[21]

> *Comment:* Regulation in the context of a thoroughly rational system, one which accurately identifies sub-standard practice and seeks to correct it through reasonable means, probably would be welcomed by the majority of physicians. But in the context of a system which frequently must seem haphazard in its selection of compensable events, it is inevitable that the resulting regulatory efforts would be viewed with great suspicion, especially if a significant part of the regulation were to come from outside the medical profession. That this suspicion would create demoralization within medical ranks, with a variety of unfavorable consequences, is obvious.

Restrictive No-Fault Systems

There are three additional approaches which have as their point of reference an unanticipated result of treatment, but in each case the compensable event is narrowly defined.

The most restrictive concept is offered by Hansen and Stromberg in a November 1969 article in the Hastings Law Review.[22] This article reviews several aspects of hospital liability and gives relatively brief mention to a no-fault system for hospital injuries. The authors define a compensable medical accident as an unexpected result, but one which would "have to refer to a result unexpected according to medical knowledge at the time of treatment." They said further that "the phrase 'unexpected result' should not be held to include infections or complications which occasionally occur from the kind of treatment administered, even though the infection or complication might occur in a very small percentage of cases." In other words, untoward results which are a calculated risk of the medical treatment would go uncompensated.

> *Comment:* Where the injury is rare, the assertion that it is a calculated risk of treatment (usually surgical) is a common defense in a professional liability action. As discussed above, almost all such injuries are medically caused although there is a sound basis for excluding compensation when the complication is truly unpreventable; for example, a toxic reaction to necessary drug therapy. But where the rare injury results from surgery, this is precisely the sort of event which all other no-fault systems compensate. And under the present tort system, recovery for these injuries is not uncommon when the plaintiff's attorney is able to show some deviation from standard care associated with the accident. Of course, where an "unexpected result" is not a calculated risk of treatment, tort liability probably will result because the physician cannot explain away the occurrence. In California *res ipsa loquitur* applies to these cases.

The second plan, which has been discussed for a number of years, involves "trip insurance" for the patient in hospital. As generally conceived, this coverage would be limited to surgical patients. In return for insurance protection which would cover any unanticipated consequence of treatment, the patient would agree not to sue the physician for negligence. Such insurance raises two preliminary questions: First, would the California Supreme Court allow this hold harmless (exculpatory) contract between doctor and patient, or would it be void as contrary to public policy. Second, even if the contract were legal, how would the parties differentiate the treatment-related injury from some adverse consequence of the patient's disease process?

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[21] Mr. Carlson is interested in a technology of outcomes analysis because he sees it as an efficient way of identifying compensable events in a no-fault system. But this technology has another application; it is being developed in anticipation of a greatly increased concern for quality of health care delivery. This concern on the part of organized medicine in California is apparent, and it is assumed that those states which are laggard will be stimulated by federal intervention as the government becomes increasingly involved in health insurance. Especially where outcomes analysis is combined with informed, even though cursory, evaluation of medical treatment process it seems apparent that reasonably adequate estimates can be made concerning competence of the care delivered. Those concerned with this technology believe that concern with treatment process can decrease as their outcomes analysis becomes increasingly refined. For those who accept the implications of control inherent in this developing technology, the inevitable lack of precision, and therefore the chance for error in a specific case, does not constitute a serious flaw. It is reasoned that careful analysis of cases which are erroneously identified as "deviations from expected results" will identify the system's error. I mention this application of outcomes analysis because its apparently reasonable application in the area of quality control may have made it seem attractive for, and applicable to, the matter of determining the compensable event in a no-fault system. But there are vital difference: First, it is not the patient's right to recovery which is being vindicated by an outcomes analysis as applied to quality control. There is not a flood of cases being processed by an administrative agency, each with an attorney asserting the validity of his client's case, many of these cases perhaps being without merit. Second, there is no need for "litigating" the standard of care issue in such cases as are described above. Most importantly, the standards applied in a quality control evaluation can be realistic and flexible. Third, the physician "charged" with a particular untoward result of treatment neither wastes time in an administrative proceeding nor is forced to defend himself in public. Finally, a quality control enterprise probably would have sufficient peer participation so that most physicians would accept these regulatory pressures with good grace. The introduction of attorneys into the no-fault system would, for many physicians, produce the opposite effect.

[22] "Hospital Liability for Negligence," The Hastings Law Journal, Vol. 21, page 1, November 1969.

The first question focuses our attention on a 1963 California Supreme Court decision, Tunkl vs. Regents of the University of California.[23] In this case the patient had signed a contract upon entering the UCLA Medical Center in 1956 which released "the Regents of the University of California and the hospital from any and all liability for the negligent or wrongful acts or omissions of its employees, if the hospital has used due care in selecting its employees." The courts found this contract invalid as contrary to the public interest. Why? It was because of the hospital's decisive bargaining strength, the practical necessity and importance of the service to the patient, and also because the contract made "no provision whereby a purchaser may pay additional reasonable fees and obtain protection against negligence."

It seems obvious then, that a bare contract which sacrifices the patient's right to sue will be invalid. But especially where the hospital paid the premium, it is interesting to speculate if adequate insurance payments for surgical injury, without regard to fault, would be considered by the California Supreme Court as a *quid pro quo* for the patient's forfeiture of his right to sue.

There remains the second question: How shall the untoward result of treatment be defined? Controversy on this question could be prolonged, as discussed above. The following partial solution has been suggested: Consider the fact that elective operation on patients who are excellent risks (who have no complicating diseases, are not elderly, and other such factors) is the background for an almost certain lawsuit where catastrophic surgical, or post-surgical, injury occurs. And it is these cases which are likely to yield the highest jury verdicts. Also, in these cases the complications probably will not be part of the patient's disease process, but rather will be treatment related. Therefore, why not ignore the causation question and only look to the result in determining whether such patients should be compensated?

A broader approach is suggested by the following plan: Upon entering the hospital the patient's physicians would write a prognosis on the chart. Where the result of treatment substantially deviated from the prognosis, the patient would have a choice of receiving no-fault compensation, and giving up his right to sue, or of pursuing his tort remedy. This approach probably would not be applicable to the particularly complicated case. And the physician's prognostic statement probably would have to be more complete than a couple of words. But the plan has the virtue of avoiding most causation questions (presumably if the patient died of an unrelated coronary occlusion, for example, this fact could be introduced to defeat compensation) and there would be no problem of validity of the contract, since the patient or his heirs would not agree to forfeiture of his tort remedy until after the injury.

Constitutional Questions

California's State Constitution does not guarantee a jury trial in civil cases, although this right is provided by statute. And the Seventh Amendment to the United States Constitution, providing for a jury trial in civil cases where the amount in litigation is more than $20, applies only to federal court cases. (It is not, like the Sixth Amendment which provides for jury trial in criminal cases, a federal constitutional protection which extends to the state courts.) Thus, the California legislature could establish no-fault liability in malpractice cases if there were no additional constitutional issue.

But there is. A no-fault system does not just deny a jury trial to the parties in a professional liability action; they are also denied access to a judicial system based on tort law and its theory of recovery. Is there a constitutional impediment to such a wholesale substitution of one system for another? It is the equal protection clause of the Fourteenth Amendment of the United States Constitution which is relevant here. This requires that a group which is selected for different treatment (that is, tort actions against physicians and hospitals are eliminated but not tort actions against others in society) must be *reasonably* selected—that is, an analysis of all of the facts must show a sound basis for the separate classification of the group, and the social benefit must outweigh the social harm incurred.

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[23] 60 Cal. 2d 92, 1963.

In speculating on the constitutionality of the no-fault liability system for medical injuries, it is useful to consider no-fault in automobile collision injuries. There the justification for legislation is abundant. Jammed calendars in metropolitan areas, steadily rising bodily injury insurance premiums, the enormous incidence of auto injuries, the comparatively small percentage of the premium dollar which goes to injured patients, all attest the reasonableness of the law. Yet, in the four or five states where it is operative the no-fault auto statutes address themselves only to the comparatively minor injuries, leaving all of the rest to the tort system.[24]

Considering the sweeping change involved in a literal no-fault system for medical injuries, it is likely the California Supreme Court would require very persuasive reasons for such a law. In a recent conversation with a Superior Court judge who is known for his scholarship in constitutional law, he repeatedly brought up the importance of thorough documentation to support the contention that serious ills would be escaped and substantial benefits gained by a no-fault system.

Social Insurance

Social insurance, also termed a social security system for compensation, is defined by its scope of application. Most narrowly, it simply means government financing of a disability insurance system, and the rules for identifying which medical injury deserves compensation might be no different than those discussed above. However, in the ordinary sense, a social insurance system for medical injury compensation would disregard all facts of the case except the fact of disability and that the disability arose in relationship to the medical treatment system.

Thus, a patient who entered the hospital with two legs and left it with one, even though the amputation was made necessary by a malignant lesion of the bone, would receive compensation. Two difficulties are immediately apparent.

First, what of the patient who suffers severe low back pain and, following surgical operation for example, finds himself no better. Since medical treatment has not increased his disability, he presumably would not be compensated. But what if he is no better because of negligent management? As the social insurance plan has eliminated tort remedy, he can receive no compensation. And what if, in fact, he is no better and no worse, but contends that he is worse? This must require an administrative proceeding, which could be quite detailed under some circumstances, in order to determine the validity of his claim.

Second, and far more important, note that it is the nexus with some feature of the community's health system that provides for the patient's ultimate financial recovery. If he has a headache, enters the hospital and leaves with hemiplegia from a stroke, he will be compensated. But if he has a headache and is treated by his wife and has a stroke at home, he will not be compensated. This is an obvious injustice for the patient but it has a far more critical effect on the medical community. A social insurance system with this inequity would force every individual with any complaint which *he thinks* might culminate in a permanent disability to obtain medical supervision. Such a system would decrease self-reliance and at the same time grossly overburden the community's health care facilities.

Rationality as well as justice in a social insurance system would seem to be achievable only by payment for every disability, regardless of the patient's medical background or relationship to some health care service. Such a feature of a welfare state is, of course, enormously expensive and social theorists have argued for and against such a final shelter from life's vicissitudes. Suffice to say that social insurance, regardless of the scope of its application, seems to most sociologists a far off prospect for American society.

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[24] From the physician's viewpoint it would make no sense to have a no-fault system covering only small medical injuries. These are seldom litigated in the current system. On the other hand, for the patient this would be a substantial benefit. Under the present system, even where there is relatively clear liability, if his loss is only one or two thousand dollars and there is no residual disability, it is not profitable for a competent malpractice plaintiff's attorney to pursue the case.

Arbitration as an Alternative to No-Fault

The well known rigors of court trial, along with the delay before a suit is finally closed, have attracted many physicians to the no-fault concept. However, arbitration can yield these benefits without the serious drawbacks of a no-fault system.[25] In fact, from the physician's viewpoint, the value of arbitration must be determined by a comparison with the tort, rather than no-fault, system.

Binding arbitration in professional liability cases was, until recently, unique to California. It has been used at the Ross-Loos Medical Group since 1931. A hospital pilot program in Southern California, co-sponsored by the California Medical Association and the California Hospital Association, has been in progress for two years. Southern California-Kaiser Health Plan has required arbitration contracts of its patients since January 1971. Private physicians have had access to arbitration through an insurance carrier, Casualty Indemnity Exchange, for the past two years.

The cases at Roos-Loos are neither sufficiently numerous nor adequately representative (a very high proportion of cases where there is a significant risk of liability are settled) to permit firm conclusions about the value of arbitration. It is virtually certain, however, that during the next two or three years enough cases will proceed through arbitration, especially in the Southern California-Kaiser experience, so that its value may be finally determined.[26]

A discussion of arbitration is outside the scope of this paper. Copies of my paper on this subject, presented at the Center for the Study of Democratic Institutions last September, are available upon request.

Discussion

A no-fault system for compensating injured persons cannot be analyzed outside the context of the injury. The compensable event for the automobile accident victim usually is obvious. For the patient who suffers an untoward result of medical treatment, it frequently must be enormously subtle. In such cases, pursuit of the question leads right back to a standard of care analysis, conflicts between experts or textbooks or both, lengthy hearings, and even the accusatory atmosphere—all of which the physician seeks to escape by finding an alternative to customary courtroom litigation.

Theorists such as R. J. Carlson have recognized this trap in a literal no-fault system, and so a result-oriented plan has been suggested. Perhaps the simplicity and utility of "outcomes analysis" as applied in medical surveys designed to improve quality of care make this approach seem applicable in identifying compensable events for a no-fault system. However, the difference between their immediate purpose and the method is crucial: For quality control the problem is to gather enough information for evaluation in order that pressures may be brought which will, ultimately, stimulate participation in continuing education, improve techniques and procedures, limit certain physicians in their scope of practice, and so on. The agency using the data, that is, the "outcomes" of treatment in a given community, probably would vary its criteria for assigning "fault" from time to time. Such questions would be relatively incidental compared to the problem of effecting improvements in medical care and gaining the cooperation of physicians in the community. Compare this to the result-oriented no-fault system.

Its immediate purpose is to compensate a patient. He brings the claim, he has an attorney, they are concerned with a "correct" (that is, favorable) application of the rules in their particular case. The physician and his attorney can be depended upon to resist the claim, especially if the consequence of repeated adverse decisions will be a limitation of the physician's scope of practice.

So precision is demanded of the result-oriented system, at least to the degree that physicians generally will not feel compensation decisions are handed down in an arbitrary manner. In a great many instances, especially where diagnostic judgments are involved and also where there are unusual circumstances associated with the treatment process, detailed analysis of the case will be required. If such analysis is not provided, then either side may regard the system as frequently unjust. Yet the required analysis leads right back to the complexities and absurdities of determining compensation in a literal no-fault system.

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[25] The term *arbitration* is used to signify "binding" arbitration as opposed to panel arbitration. The former is permitted by law in 26 states, is a substitute for courtroom litigation, and permits only a limited appeal from the arbitrator's decision. The latter is usually advisory only, with the panel's decision placing no obligation on either party, although a decision for the plaintiff is associated with the guarantee of a medical witness in case settlement is not achieved. Binding arbitration requires a contract between the parties (usually achieved before establishing the treatment relationship) whereas the agreement to arbitrate before a panel arises after the injury.

[26] HEW's Commission on Medical Malpractice has ordered a study of both panel and binding arbitration. The results will be available this year.

Limited no-fault systems carry a certain appeal. Trip insurance for the uncomplicated case, especially in a relatively young patient undergoing elective surgical operation, is considered rational by many observers. It is dramatic complications associated with that sort of case that account for a good proportion of very high jury verdicts and settlements.

Financing of a comprehensive no-fault system would be prohibitive. An objective of no-fault compensation in the automobile and industrial accident field is to transfer as much of the premium dollar as possible to the injured party. But, for reasons stated, a comprehensive no-fault approach for medical injuries would lead to extensive hearings in a large number of cases.

It is worth re-emphasizing that patients ordinarily do not enter the continuum of medical care unless they are ill. In a literal no-fault system it would be easy for patients to regard a less than satisfactory outcome of treatment (and this is in terms of their own expectations, which might be unrealistic) as a basis for compensation. Especially would this be true if there were significant disability. Unmeritorious claims could drown the system in administrative proceedings. A result-oriented system might reduce the number of claims, but this is only speculative. Limitations on the patient's right to a detailed analysis of the treatment process should permit the hearing officer to dispose more easily of the invalid claims. However, as discussed above, rules providing ease of administration would virtually guarantee dissatisfaction with the "unjust" result in a significant number of cases. Thus, in order to avoid arbitrariness, detailed treatment analysis would be necessary in many cases, leading right back to the complications which a system of outcomes analysis is designed to obviate.

I have avoided a discussion of social philosophy. It may be enough to point out that an imposition of absolute liability for manufacturers and food producers expresses a growing attitude that those who are injured should be compensated and those who can distribute the cost of insurance should be burdened with payment. Equally important, such a rule is widely accepted as contributing to greater care on the part of the producer. It is plain to physicians that there is not the remotest analogy between an industrialist and the private practitioner. But if comprehensive federal health insurance is followed by an increasing number of health maintenance organizations, perhaps medicine some day will be regarded as far more monolithic than it is at present. At that time will special burdens, of the sort discussed here, be placed on physicians?

Social theorists make it plain that quality control, rather than patient indemnification, is the most important goal in a no-fault system for adverse medical results. Broad and effective action by the medical profession to initiate peer evaluations and controls would reduce those pressures which may develop in the future for a no-fault system.

It is important to make a final point, although it is one which is difficult to quantitate or even describe. Physicians appreciate as almost no others can the difficulties and psychological stress which are involved in medical decision making. It is currently fashionable to feel little sympathy with this professional group who have been in a seller's market for many years and who, while admittedly working long hours, enjoy a level of income which is generally regarded as very high even in these inflated times. It is easy for critics to forget that good medical practice requires the freedom to make choices with only medical considerations in mind. These choices are often difficult. The physician, in retrospect, sometimes may realize that alternative choices would have avoided serious disability or even death. Yet the possibility for such unfavorable outcome of a given decision is faced by most physicians frequently. To the extent that the medical community develops the feeling they are being subjected to unwarranted interference in the conduct of their profession, this sense of harassment cannot but interfere with medical decision making.

Frederick B. Hodges, M.D., Chief Deputy Director, State Department of Public Health

Chronic Hemodialysis In California

Chronic renal disease accounts for about one percent of all deaths in California or about 1500 annually. A special study of 1968 death certificates of persons dying of chronic renal disease indicated that 675 under age 65, or about 33 patients per million population per year, could have benefited from chronic hemodialysis or renal transplantation or both.

The number of chronic hemodialysis patients served annually in certified chronic hemodialysis facilities in California rose from about 800 in 1970 to about 1350 in 1971, a net increase of about 28 patients per million population.

Chronic hemodialysis facilities in California have been increasing rapidly, particularly during the last few years. The number of certified civilian facilities increased from 39 in December 1970 to 59 in March 1972. The State Department of Public Health certifies qualified facilities desiring reimbursement for the care of State-supported patients. Chronic hemodialysis facilities submitting an application are visited by a team, including a consultant who is an expert in nephrology, to determine if the facility is in compliance with the "Standards for Facilities Providing Chronic Hemodialysis" established on the recommendation of an expert advisory committee. Facilities are recertified annually.

Of the 59 facilities, 21 qualify as Renal Dialysis Centers, which are hospitals providing a full range of medical services for patients with renal disease. The remaining 38 are designated as Community Hemodialysis Units which offer primarily chronic hemodialysis. About three-fourths of these units are in hospitals. The others have been established for medically stable patients who cannot be home-trained but who can be dialyzed at lower cost in an out-of-hospital facility. About three-fourths of all dialysis facilities provide home training opportunities for patients who can be taught with a family member to carry out their treatment at home. About one-fourth to one-half of chronic hemodialysis patients can be home-trained. In March 1972 there was one chronic hemodialysis facility for each 300,000 population and one chronic hemodialysis bed for every 50,000. Los Angeles, Orange and San Francisco counties have the greatest number of facilities and beds per million population. The State Department of Public Health has also certified 15 renal transplantation facilities desiring reimbursement for state-supported patients.

Over two-thirds of all chronic hemodialysis patients served in certified facilities in 1971 received financial assistance for chronic hemodialysis treatment from the state. This treatment is so expensive that very few patients are able to pay for it for very long. Most of them must eventually seek state assistance through Medi-Cal, Crippled Children Services, or the four State Renal Centers which receive state grants. Recently Mercy Hospital in Bakersfield and Martin Luther King, Jr. Los Angeles County General Hospital received the state grants authorized by the 1970 legislature for programs to train patients and their families to carry out their own hemodialysis treatment at home. Both the areas served by these hospitals have a higher rate of chronic renal disease than the state as a whole.

Chronic hemodialysis facilities appear to be adequate to take care of the present demand.

However, these facilities are not necessarily distributed evenly. Some areas are oversupplied and others undersupplied. To insure the need for each new facility desiring certification, the areawide Comprehensive Health Planning agencies have been asked to review the need before an application for certification is accepted.

Patients leave chronic hemodialysis by successful renal transplantation or by death. Although renal transplantation has been increasing remarkably in California—more than 1000 patients have received one or more renal grafts in civilian hospitals in California since 1957—it has not been able to keep up with demand. Four hundred forty-eight chronic hemodialysis patients were on transplantation waiting lists December 31, 1971, according to the records of the certified dialysis facilities. Of these, 406 were waiting for cadaver kidneys and the remainder had made arrangements with live donors. These figures indicate the great need to make available more cadaver kidneys. The public should be better informed so they can make the arrangements for kidney donation after death, as provided for in California's Uniform Anatomical Gift Act. Even more important, all physicians should take responsibility for identifying their dying patients who could donate kidneys. These physicians should make certain that this opportunity is presented to the families in time to make the necessary arrangements with a renal transplant service.

For further information about chronic hemodialysis and renal transplant facilities, physicians may write the Kidney Disease Program of the California State Department of Public Health, 2151 Berkeley Way, Berkeley, Ca. 94704.

FOREIGN BODY AIRWAY OBSTRUCTION

How do you handle the patient with partial airway obstruction due to a foreign body?

I would stress that a patient with a marginal airway should be supported with oxygen, reassured, and calmed, and that nothing further be done until the proper equipment is available. Possible catastrophes could be inflicted by the well-intended assistant. The probing finger may impact the foreign body, either into the larynx or into the esophagus by pushing it down; turning the child upside down and slapping him on his back can do the same thing. The foreign body that is freely moving about the tracheobronchial tree may be directly wedged with gravity and a tussive blast into the vocal cords, creating a sudden acute impaction. Where a foreign body is suspected as being the obstructive agent, manipulation should be done only under controlled circumstances, that is, where a laryngoscope, bronchoscope, and proper extracting forceps are available.

—JOHN A. TUCKER, M.D., Philadelphia

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Information

CLINICAL CARDIOLOGY SERIES

The Stokes-Adams Syndrome

Robert A. O'Rourke, m.d.

Material Supplied by the American Heart Association

Part I—Definition and Etiology

The Stokes-Adams syndrome is defined as an abrupt, transient loss of consciousness due to sudden but pronounced decrease in the cardiac output, which is caused by a sudden change in the heart rate or rhythm. This definition does not include vasovagal syncope or epilepsy although patients with Stokes-Adams syncope may have seizures during periods of cerebral ischemia. Although partial or complete heart block is usually present during asymptomatic periods, many arrhythmias may produce syncopal episodes with or without the presence of previously established complete heart block. "Arrhythmia-induced syncope" is a more specific term and includes the primary cause of the decreased cerebral blood flow.

Clinical Features

The clinical manifestations of arrhythmia-induced syncope depend upon the duration and type of underlying arrhythmia as well as the status of the cerebral circulation. Symptoms of arrhythmia-induced syncope vary from slight faintness to loss of consciousness, with or without convulsions.

Characteristically, during the attack there is an initial pallor. Following resumption of the normal circulation there is usually a facial flush due to reactive hyperemia. The absence of an aura tends to separate seizures occurring during Stokes-Adams syncope from seizures of primary cerebral origin. Stokes-Adams seizures usually commence and terminate abruptly. The patient may resume a previous conversation or activity without being aware of the pause produced by the period of arrhythmia-induced cerebral ischemia. A slow or very rapid pulse during the period of unconsciousness points toward the correct diagnosis. Electrocardiographic monitoring during a syncopal episode demonstrates the responsible rhythm and makes appropriate therapy possible.

Etiology

Since most patients with arrhythmia-induced syncope have some impairment of atrioventricular (A-V) conduction either during or between attacks, the causes of Stokes-Adams syncope are often the causes of complete heart block.

Structural Lesions of the Heart. Approximately 7 percent of the cases of complete heart block in adults are congenital in etiology, with or without associated cardiac defects. Syncopal episodes complicating congenital heart block are uncommon but do occur and may necessitate pacemaker insertion.

Myocarditis of various causes may involve the conduction system, resulting in complete heart block and syncopal episodes. Diphtheria has long been known to be associated with conduction defects, particularly complete heart block.

Heart block, occasionally with Stokes-Adams syncope, has been reported during the course of connective tissue disease and in association with degenerative skeletal muscle and nervous system disorders. In valvular heart disease valve calcification or endocarditis may involve the conduction system and produce incomplete or complete heart block.

Acute myocardial infarction is complicated by complete heart block in approximately 2 to 7 percent of cases. Complete heart block complicating inferior wall myocardial infarction usually proves to be transient and restoration of normal conduction occurs within two to three weeks. The conduction defect involves the A-V junctional tissue. When an anterior wall infarction is the cause of complete heart block the mortality rate is extremely high even with pacemaker insertion. In this situation the complete heart block is fre-

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quently due to extensive myocardial necrosis involving the right bundle and the two divisions of the left bundle (trifascicular block) rather than to a conduction defect in the A-V junction.

In a considerable number of patients no cause can be established for complete heart block. Careful pathological examination has shown that many such patients with heart block do not have extensive coronary artery disease but have areas of fibrosis involving the conduction system distal to the common bundle (trifascicular block), either alone or in association with scattered areas of fibrosis throughout the myocardium. In elderly people this has been attributed to "sclerosis of the left side of the cardiac skeleton" which presumably results from wear and tear due to the repeated pull of the contracting left ventricular musculature.

Primary and metastatic neoplastic disease, metabolic disease and infiltrative disorders of the myocardium may produce heart block. Complete heart block is a potential risk during corrective heart surgery, particularly during repair of ventricular septal defects. Surgical heart block frequently reverts to sinus rhythm within three to four weeks following operation. If it continues beyond this period a permanent pacemaker is usually inserted. Non-penetrating chest injury is an occasional cause of complete heart block.

Heart block has been reported in association with Reiter's syndrome, amyloidosis, Paget's disease and sarcoidosis. The myocardium is involved in approximately 20 percent of autopsy-proved cases of sarcoidosis. Conduction disturbances, Stokes-Adams syncope and sudden death are known to occur in sarcoidosis and this entity is an important consideration in the differential diagnosis of acquired complete heart block in young adults.

Electrolyte Disorders. Potassium is the most important electrolyte in relation to A-V conduction. Isolated instances of advanced A-V block have occurred in patients during or following the admission of large doses of potassium salts. Hyperkalemia decidedly decreases the ventricular rate in pre-existing heart block.

Acidosis depresses the ventricular pacemaker in complete heart block and may precipitate Stokes-Adams syncope. Alkalosis, hypokelemia and hypernatremia increase A-V conduction and may reverse heart block. However, alkalosis and hypokalemia may increase ventricular ectopic activity, leading to ventricular tachycardia or fibrillation.

Toxic Effect of Drugs. Digitalis is the drug most frequently responsible for producing complete heart block. Syncopal episodes are uncommon during heart block due to digitalis toxicity because the ectopic pacemaker frequently originates in A-V junctional tissue and the ventricular rate is faster than in complete heart block of other cause. The supraventricular rhythm in patients with digitalis toxicity is often atrial fibrillation.

The antiarrhythmic agents quinidine and procaineamide depress the conduction system as well as pacemaker rhythmicity and are contraindicated in complete heart block. Diphenylhydantoin and lidocaine may also depress the ectopic pacemaker and are therefore contraindicated in the presence of high degree A-V block. However, any of these antiarrhythmic drugs may be safely employed to suppress premature contractions in the presence of heart block if an adequately functioning electrical pacemaker has been inserted.

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Part II—Mechanisms and Treatment

During the past few years improved cardiac monitoring has more precisely elucidated the underlying electrocardiographic mechanisms producing Stokes-Adams syncope. Moreover, the rapid advances in electrical pacemakers have contributed significantly to the prevention of arrhythmia-induced syncope.

Electrocardiographic Mechanisms

At one time ventricular standstill was thought to be the sole mechanism responsible for Stokes-Adams syncope and it is still considered the most frequent underlying rhythm disturbance. However it is now established that Stokes-Adams attacks may also be due to extreme bradycardia or to a variety of tachyarrhythmias, particularly ventricular tachycardia and ventricular filbrillation. Continuous monitoring has demonstrated that several electrocardiographic mechanisms may produce syncope in the same patient.

The arrhythmias responsible for Stokes-Adams syncope may be divided into seven groups:

1. *Sudden interruption of atrioventricular impulse transmission causing transient asystole.* When the cardiac rhythm changes from a sinus mechanism or incomplete A-V block to complete heart block, a period of asystole often occurs before the junctional or ventricular pacemaker assumes rhythmicity at its inherent rate. This "warm-up period" varies from ten to ninety seconds and is termed the "preautomatic pause."

2. *Atrial standstill with failure of the junctional pacemaker resulting in ventricular asystole.* When sinoatrial node impulse formation ceases and the A-V junctional tissue fails to assume rhythmicity, ventricular asystole results. This mechanism for Strokes-Adams syncope may occur in patients with inferior wall myocardial ischemia and may be influenced by vagal hyperactivity. This is an uncommon mechanism of arrhythmia-induced syncope.

3. *Asystole in the presence of established heart block.* This arrhythmia may result from a shift in the pacemaker below the area of nonconduction to still a lower focus resulting in a period of asystole resembling the "preautomatic pause."

4. *Paroxysmal ventricular tachycardia or fibrillation in the presence of complete heart block.* A slow heart rate during complete heart block predisposes to rapid impulse formation from ectopic foci. Either ventricular tachycardia or fibrillation may then ensue with syncope resulting.

5. *Paroxysmal ventricular tachycardia or fibrillation during normal A-V conduction.* These arrhythmias are most frequently observed in patients with acute myocardial infarction but have also caused syncopal episodes in patients with apparently normal hearts.

6. *Supraventricular arrhythmias.* Supraventricular tachycardias and bradycardias associated with syncopal episodes have been demonstrated by continuous electrocardiographic monitoring in many patients with the Stokes-Adams syndrome. Frequently the sinus bradycardia predisposes to episodic supraventricular tachycardia ("bradycardia-tachycardia syndrome"). In patients with coronary artery disease tachycardia increases myocardial oxygen demands and decreases left coronary artery diastolic blood flow, often decreasing cardiac output despite the increase in heart rate. Syncopal episodes may result.

Sinus bradycardia, sinoatrial block and sinoatrial arrest may cause syncope in patients with heart disease who are unable to increase stroke volume sufficiently to maintain adequate cerebral blood flow.

7. *Combined forms.* Uncommonly, paroxysmal tachyarrhythmias may be followed by a period of asystole due to a delay in automaticity of pacemakers which have been suppressed during the tachycardia.

The recognition that different electrocardiographic mechanisms may produce syncope in the same patient on different occasions is important in therapy.

Treatment

The aim of therapy for arrhythmia-induced syncope is threefold: (1) prompt restoration of the circulation during cardiac arrest, (2) restoration of an intrinsic cardiac rhythm adequate to maintain cerebral blood flow and (3) prevention of recurrent episodes.

Medical Treatment. The medical therapy of complete heart block includes the correction of potential contributing factors such as acidosis and hyperkalemia. The sympathomimetic drugs, which include parenteral epinephrine, oral ephedrine and isoproterenol by either route of administration, are primarily indicated when ventricular asystole or bradycardia occurs in complete heart block and intracardiac pacing is unavailable. These agents act by increasing A-V conduction, increasing the rate of the ventricular pacemaker, and shifting the lower pacemaker to a higher focus in the common bundle or A-V junctional tissue. During an attack of arrhythmia-induced syncope due to bradycardia, isoproterenol should be given by intravenous infusion during electrocardiogram monitoring so that its administration can be rapidly terminated if ventricular irritability results.

The vagalytic agent atropine may increase the ventricular rate in complete heart block complicating a recent inferior wall myocardial infarction. Atropine is often successful in the treatment and prevention of Stokes-Adams syncope due to sinus bradycardia, sinoatrial block and bradycardia-tachycardia syndrome.

Steroids through their anti-inflammatory and hypokalemic effects have been occasionally successful in improving A-V conduction in patients with complete heart block due to myocarditis or acute myocardial infarction.

The trisodium salt of ethylenediamine tetraacetic acid, a calcium-chelating agent, has been used in the treatment of complete heart block due to digitalis intoxication when electrical pacing is unavailable.

Pacemaker therapy. Because of the unpredictable, potentially fatal nature of Stokes-Adams attacks and the inconsistent results and frequent complications with drug therapy, electrical pacing has become the treatment of choice when syncope occurs in patients with complete heart block.

The general indications for pacemaker insertion include (1) complete heart block associated with congestive heart failure (2) complete heart block with Stokes-Adams syncope (3) complete heart block following acute anterior or inferior wall myocardial infarction (4) partial A-V block (second degree block) complicating anterior wall myocardial infarction and (5) post-surgical complete heart block.

Recent reports have demonstrated the feasibility of suppressing episodes of ventricular tachycardia and fibrillation in patients with normal A-V conduction by pacing the atrium or the ventricle at a rate faster than that present between episodes of ventricular tachyarrhythmia. Electrical pacing has been employed successfully in combination with propranolol and cardiac sympathectomy in the treatment of otherwise unresponsive ventricular arrhythmias. Rapid atrial pacing has been used successfully in the treatment of supraventricular tachycardias including atrial flutter and paroxysmal atrial tachycardia.

In patients with syncopal attacks due to ventricular tachycardia or ventricular fibrillation complicating complete heart block, the emergency insertion of a ventricular pacemaker is strongly indicated. A ventricular pacemaker is the only means available for the long-term prevention of ventricular tachyarrhythmias in patients with heart block. If transient ventricular asystole complicates complete heart block a ventricular pacemaker is also indicated. A single Stokes-Adams attack in a patient with complete heart block is sufficient reason for pacemaker insertion.

Selected Items from the FDA Drug Bulletin

Nitroglycerin Packaging Affects Potency

A recent FDA assay survey of nitroglycerin tablets suggests that improper packaging has a crucial bearing on the drug's stability and potency.

The assay involved nitroglycerin tablets stored in a pen-shaped plastic container provided by pharmacies as a convenient means of carrying several days' supply. Dispensers containing the drugs were left standing at room temperature for 1-, 2-, and 3-day periods.

The nitroglycerin was found to have decreased to about 50 percent, 30 percent and 20 percent of initial potency after being left in the dispensers for these periods. FDA has requested recall of the dispensers.

The assay led FDA to conclude that unexplained patterns of therapeutic response by patients to nitroglycerin therapy may be caused by the manner in which the drug is packaged. Physicians should consider this possibility when evaluating patient response to the drug.

To avoid rapid loss of potency, nitroglycerin should be kept at all times in tightly-sealed glass vials. Physicians and pharmacists may wish to tell patients this when prescribing and dispensing the drug.

—FDA Drug Bulletin, Feb 1972

* * *

Imipramine and Alleged Birth Defects

Recent alarm about possible implication of imipramine (Tofranil®), an anti-depressant drug, in birth defects (amelia and phocomelia) appears to be without firm foundation. A report of an association between imipramine given pregnant mothers and congenital deformities in their offspring came from Australia in early March.

The Australian Department of Health recently informed FDA that it regards as inconclusive the data on which the report was based. In addition, the Department of Health and Social Security in London told FDA that during the eight years the British Committee on Safety of Drugs has been in operation, only one report of congenital abnormality of a limb associated with imipramine has been received. Amelia and phocomelia occasionally occur without known association with drugs.

FDA-approved imipramine labeling in use since 1965 contains the following warning: "Safe use of imipramine during pregnancy and lactation has not been established; therfore, in administering the drug to pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results. There have been clinical reports of congenital malformation associated with the use of this drug, but a causal relationship has not been confirmed."

—FDA Drug Bulletin, May 1972

* * *

Iodochlorhydroxyquin and Travelers' Diarrhea

The Food and Drug Administration recommends that iodochlorhydroxyquin (Entero-Vioform®) not be given to prevent "travelers' diarrhea."

FDA's conclusion is based on recent findings in Japan, Australia and Sweden implicating iodochlorhydroxyquin as the cause of a frequently severe neurologic complex, subacute myleo-optic neuropathy (SMON). Evidence is not yet available to confirm this association, but it appears that too-long-continued dosing with iodochlorhydroxyquin may be a major factor in SMON.

There is no acceptable evidence that other halogenated hydroxyquinolines, chiniofon and diiodohydroxyquinoline (Diodoquin®), are effective in the treatment of prevention of "travelers' diarrhea."

Travelers to areas where hygiene and sanitation are poor may be able to prevent diarrhea by eating only recently peeled or thoroughly cooked foods, and by drinking only boiled or bottled water, bottled carbonated soft drinks, beer or wine. Tap water used for brushing teeth or for ice in drinks may be a source of infection. The cause of the diarrhea is uncertain.

Most tropical disease specialists believe iodochlorhydroxyquin is ineffective for "travelers' diarrhea." Labeling of the product cites only intestinal amebiasis as an indication.

—FDA Drug Bulletin, May 1972

* * *

Methadone for Heroin Addiction

FDA plans to sanction increased use of methadone as a substitute for heroin. Maintenance treatment of patients 18 years and older with oral dosage forms of methadone will be available at about 450 Drug Addiction Centers throughout the United States. Each center is being inspected by health officials and is subject to FDA approval.

To control illicit traffic in methadone, the drug will be available only in approved centers and hospital pharmacies. Accurate record-keeping for the drug will be required. These restrictions do not prohibit use of methadone in the treatment of severe pain or for detoxification of addicts in hospitals.

Methadone taken by mouth prevents heroin withdrawal symptoms and, in general controls the intense desire or need for heroin. Addicts who stay on methadone maintenance programs are often able to return to a normal life pattern.

FDA's decision was made after consultation with the National Institute of Mental Health and the Justice Department's Bureau of Narcotics and Dangerous Drugs, and was endorsed by The Special Action Office for Drug Abuse Prevention of the White House. FDA also had the advice and opinion of many other groups, such as the AMA's Council on Mental Health. The consensus is that current evidence on the safety and effectiveness of methadone is sufficient to permit its use for narcotic addiction in adults.

—FDA Drug Bulletin, May 1972

In Memoriam

CARUSO, TENERO DANNY, Los Angeles. Died April 20, 1972 in Los Angeles of chronic lymphatic leukemia, aged 66. Graduate of St. Louis University School of Medicine, 1931. Licensed in California in 1932. Doctor Caruso was a member of the Los Angeles County Medical Association.

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DAVIS, NATHANIEL A., Los Angeles. Died April 29, 1972 of heart disease, aged 62. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1933. Licensed in California in 1933. M.D. degree from California College of Medicine, 1962. Doctor Davis was a member of the Los Angeles County Medical Association.

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HOWARD, FREDERICK S., San Francisco. Died May 18, 1972 in San Francisco, aged 58. Graduate of University of California Medical School, Berkeley-San Francisco, 1940. Licensed in California in 1940. Doctor Howard was a member of the San Francisco Medical Society.

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HOWE, J. WILLOUGHBY, Los Angeles. Died May 4, 1972 in Glendale of heart disease, aged 77. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1917. Licensed in California in 1918. M.D. degree from California College of Medicine, 1962. Doctor Howe was a member of Los Angeles County Medical Association.

⁂

KALLER, MARSHALL B., Los Angeles. Died April 26, 1972 in Long Beach of Gram negative sepsis, aged 60. Graduate of Marquette University School of Medicine, Milwaukee, 1937. Licensed in California in 1939. Doctor Kaller was a member of the Los Angeles County Medical Association.

⁂

KISER, AVONIA E., Napa. Died May 1, 1972 in Napa, aged 81. Graduate of the University of Louisville School of Medicine, 1915. Licensed in California in 1925. Doctor Kiser was a retired member of the Napa County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

KROSHINSKY, MILTON, La Mirada. Died May 6, 1972 in Whittier of cancer, aged 50. Graduate of Philadelphia College of Osteopathy, Philadelphia, 1946. Licensed in California in 1950. M.D. degree from California College of Medicine, 1962. Doctor Kroshinsky was a member of the Los Angeles County Medical Association.

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METTIER, STACY R., SR., San Francisco. Died May 19, 1972, aged 74. Graduate of University of California Medical School, Berkeley-San Francisco, 1926. Licensed in California in 1926. Doctor Mettier was a member of the San Francisco Medical Society.

O'BRIEN, ALICE BEPLER, San Francisco. Died May 2, 1972 in San Francisco, aged 74. Graduate of University of California Medical School, Berkeley-San Francisco, 1929. Licensed in California in 1929. Doctor O'Brien was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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SILIPO, ANTHONY A., Weimar. Died May 1, 1972 in Weimar, aged 54. Graduate of University of Southern California School of Medicine, Los Angeles, 1948. Licensed in California in 1948. Doctor Silipo was a member of the Placer-Nevada County Medical Society.

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SMITH, ELMER WILLIAM, Stockton. Died March 21, 1972, aged 88. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1915. Licensed in California in 1915. Doctor Smith was a retired member of the San Joaquin County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

STACK, GERALD A., Lynwood. Died May 9, 1972 in Downey of aneurysm, aged 56. Graduate of University of Cincinnati College of Medicine, 1942. Licensed in California in 1946. Doctor Stack was a member of the Los Angeles County Medical Association.

⁂

THURBER, PACKARD, SR., Los Angeles. Died May 4, 1972 in Los Angeles of metastatic carcinoma, aged 81. Graduate of College of Physicians and Surgeons, Medical Department, University of Southern California, 1912. Licensed in California in 1912. Doctor Thurber was a member of the Los Angeles County Medical Association, a life member of the California Medical Association, and a member of the American Medical Association.

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WASHKO, PETER JOHN, Carmichael. Died April 28, 1972, aged 57. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1939. Licensed in California in 1947. Doctor Washko was a member of the Sacramento County Medical Society.

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WHALLEY, RAYMOND, Los Angeles. Died May 5, 1972 in Burbank of major myocardial infarction, aged 61. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1938. Licensed in California in 1938. M.D. degree from California College of Medicine, 1962. Doctor Whalley was a member of the Los Angeles County Medical Association.

BOOK REVIEWS

California Medicine does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CARDIOLOGY—A Clinicophysiologic Approach—Edited by Stephen M. Ayres, M.D., Director, Cardiopulmonary Laboratory, St. Vincent's Hospital and Medical Center of New York; Associate Professor of Clinical Medicine, New York University School of Medicine; John J. Gregory, M.D., Assistant Director, Cardiopulmonary Laboratory, St. Vincent's Hospital and Medical Center of New York; Asst. Professor of Clinical Medicine, New York University School of Medicine; With the assistance of Meta E. Buehler, B.S., R.N., Administrative Coordinator, Cardiopulmonary Laboratory, St. Vincent's Hospital and Medical Center of New York. Appleton-Century-Crofts, Educational Division/Meredith Corporation, 440 Park Ave., South, New York City (10016), 1971. 667 pages, $15.00.

The past decade has seen almost explosive expansion of our knowledge of cardiovascular diseases. The authors' objective of reviewing this information clearly and concisely to enable the practicing physician to treat patients according to sound physiologic principles is indeed laudable. Unfortunately, the present effort falls far short of the mark. The text attempts a broad survey of cardiology and uses the format of the standard cardiology book.

The initial chapters on manifestations of cardiac diseases and the later chapters on pregnancy and the heart, cardiac tumors, and cardiac trauma are so superficial that they are virtually superfluous. The strongest chapters are on cardiac function and abnormal ventricular function; a real effort is made to simplify difficult concepts and to relate these concepts to the pathogenesis of disease. Unfortunately, even in these sections (and this is equally true for every chapter), controversy is circumvented and the reader is left with a highly oversimplified, rather dogmatic presentation.

The section on "phonocardiography and other graphic techniques" is seriously dated and incomplete. Newer concepts regarding the genesis of heart sounds, the pathogenesis and clinical importance of late systolic clicks and murmurs as well as the use of graphic techniques in differentiating patients with supravalvular, valvular, and subvalvular aortic stenosis are omitted. Similarly, there is no mention of the technique and usefulness of systolic time intervals or of the use of apex cardiography in the diagnosis of ventricular aneurysms and valvular or constrictive myocardial disease. Incredibly enough, there is no mention of the clinical usefulness of echo cardiography.

The sections on electrocardiography, diagnosis of arrhythmias, and therapy of cardiac arrhythmias give the reader little insight into basic electrophysiologic concepts, consisting only of a list of facts. Rational use of antiarrhythmic agents demands some familiarity with their cellular and monophasic action potential as well as with the importance of automaticity and re-entry in the genesis of arrhythmias. The effects of drugs and/or electrolyte abnormalities on resting and threshold potentials, conduction velocity, refractory period, and membrane responsiveness are given scant or no mention.

In summary, the present textbook cannot be recommended either for beginners or for internists seeking a resource monograph. The currently available standard cardiologic texts are broader in scope and of greater depth than the present effort. In the next revision the authors should narrow the scope of the book, focusing on the physiology, pathophysiology, diagnosis, and treatment of the more common cardiac ailments.

Melvin Scheinman, M.D.

* * *

HANDBOOK OF OBSTETRICS AND GYNECOLOGY—Fourth Edition—Ralph C. Benson, M.D., Professor of Obstetrics and Gynecology and Chairman, Department of Obstetrics and Gynecology, University of Oregan Medical School Hospitals and Clinics, Portland. Lange Medical Publications, Drawer L, Los Altos, Ca. (94022), 1971. 775 pages, $6.50.

In this pocket-size edition, the author succeeds in his intent to provide a concise and current digest of material pertinent to good obstetrical practice. The section on obstetrics is well written and includes chapters on contemporary topics such as therapeutic abortion, sterilization, and emotional aspects of pregnancy.

The gynecology chapters provide a more than adequate summary of the basic principles of gynecologic care. Included in this section is a review of pertinent aspects of infertility in both the male as well as the female. At the opposing end of the spectrum is a discussion of methods of contraception, including that of the intrauterine device.

Professor Benson has wisely recognized the importance of medical genetics and his chapter on this topic is timely. Although it is brief, it provides basic definitions, a discussion of the common hereditary disorders, and a discussion of problems associated with intersexuality.

While this book was never meant to be a substitute for a complete textbook, it is an extremely useful synopsis for the busy practitioner.

Arthur I. Goldstein, M.D.

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BECKER-SHAFFER'S DIAGNOSIS AND THERAPY OF THE GLAUCOMAS—Third Edition—Allan E. Kolker, M.D., Associate Professor of Ophthalmology and Associate Director of the Glaucoma Center, Department of Ophthalmology, Washington University School of Medicine, St. Louis; and John Hetherington, Jr., M.D., Assistant Clinical Professor of Ophthalmology and Associate Director of the Glaucoma Center, University of California Medical Center, San Francisco. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, Mo. (63103), 1970. 495 pages, with 383 illustrations and 6 color plates, $25.00.

This third edition of the Becker-Shaffer text has been revised to include the latest information on glaucoma which has accumulated over the past five years. This includes the renewed interest in cupping of the optic disc as an early sign of progression of the glaucomatous process. Flourescein angiography in relation to glaucoma is treated in detail. Static perimetry, topical corticosteroid testing and an entire section on microsurgery of the outflow channels are of special interest to the ophthalmic surgeon.

This text is readable and is highly recommended.

R. M. Sinskey, M.D.

THE COMPLETE HANDBOOK FOR MEDICAL SECRETARIES AND ASSISTANTS—Robert Lee Dennis, M.D., Director, Department of Pathology; and Director and Instructor, Medical Technology School, San Jose Hospital, San Jose, Ca.; Jean Monty Doyle, R.R.L., Director, San Jose Medical Personnel and Secretarial Agency; Former Secretary, Medical Advisory Committee, Medical Assistants Program, San Jose City College, San Jose, Ca.; Member, American Medical Record Association; Medical Illustrations by Kathryn Coburn. Little, Brown, and Company, 34 Beacon Street, Boston (02106), 1971. 576 pages, $9.50.

In order to evaluate this text and write a fair review I enlisted the help and interpretative opinions of two medical assistants, Mrs. Wini Schwartz and Mrs. Ann Shell. Both are certified medical assistants with many years of experience in their field.

To say that any book or text is a "complete handbook" is a misnomer. Keeping in mind the various roles and functions of the medical assistant, this book falls short of covering the field especially if it was intended for use in a physician's office. It is primarily hospital oriented and might be of some value in that environment with alterations, but then it would require a new title.

It is a difficult and cumbersome text to read. The illustrations are good but rather limited.

This handbook touches upon office assisting, briefly, in chapters 1, 3, 4, 5 and 7. Chapter 2 (Emergency First Aid) seems out of sequence since it appears between "Office Orientation" and "Secretarial Skills." Chapter 6 (Hospital Department) does not seem relevant to duties in a physician's office. Pages 81-315 which encompass chapters 8 and 9 (Medical Terminology, Anatomy and Physiology) would seem better placed to the back of the book. Chapter 10 (Clinical Laboratory) and chapter 11 (Radiology) would be very useful in the physician's office since they are quite comprehensive in dealing with the names of tests, description and method of collection of specimens and instructions to the patient for laboratory procedures and x-ray examinations. These chapters would seem better situated toward the front of the text. Chapter 12 (The Physician) might be meaningful to new medical assistants and would lend to a more comfortable location in the front of the handbook. Chapter 13 (The Medical History and Physical Examination) would best be located with the five chapters noted above dealing with office assisting. Pages 393-490, which is chapter 14 (Medical Reports) would be of value to a transcriber in a hospital transcribing pool.

This handbook does not compare favorably with other texts, some of which are excellent volumes, as a reference for in service medical assistants and secretaries.

Most other textbooks do not purport to cover all aspects of medical assisting, however this one seems to as stated on its cover. . . . "The most complete book of its kind, this practical handbook offers a single comprehensive source of essential information, tailored specifically to meet the need of medical secretaries and assistants."

One should not be misled by the use of the words "complete handbook" in titles . . . in most cases it is pure presumption on the part of the authors, neither of whom, in this particular case, come in direct contact with usual medical office practice.

PEARY B. BERGER, M.D.

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ATLAS OF TRANSBRONCHIAL BIOPSY—Early Diagnosis of Peripheral Pulmonary Carcinomas—Eitaka Tsuboi, M.D., Chief of Diagnosis Division, Department of Radiology, National Cancer Center Hospital. The Williams & Wilkins Company, 428 E. Preston, Baltimore, Md. (21202), 1970. 151 pages, $34.00.

This excellent treatise should be read by every pulmonary disease oriented physician and surgeon. It is featured by unusual clarity of writing and beautiful well-selected illustrations and photographs. There is a delightful accuracy of presentation wherein nothing is left out, and nothing irrelevant is added. The order and arrangement of the presentation is faultless. The reasons for the studies and manipulations are well outlined, the techniques are given step-by-step in precise detail, and results are simply presented.

In essence, this book is directed towards the early diagnosis of bronchogenic carcinoma, or as they describe it, the diagnosis of early carcinoma at a curable stage.

It is pointed out that tumors in the hilar areas cannot be found at an early stage by radiologic examinations and their discovery depends upon development of symptoms such as hemoptysis or cough followed by bronchoscopic examinations and cytology.

On the other hand lung field carcinoma can be revealed at an asymptomatic stage by appropriate x-ray examination but a cytological diagnosis of an abnormal shadow is of paramount importance. This can be accomplished by trans-bronchial biopsy following a bronchographic study which is necessary to demonstrate the involved bronchus or bronchi. The technique involves catheterization of the involved bronchus enabling a curettement of the lesion for a biopsy. An 80 percent positive cytologic diagnosis can be obtained.

They state that biopsy of the single lesion takes approximately 20 minutes during which time the examiner's hands are exposed under x-ray television to a total of 20 r R/h. They believe this is a nominal radiation exposure but advise strict protective measures.

Two criticisms can be offered. Quite a number of these lesions are of a size that could be more expeditiously diagnosed by needle aspiration biopsy. This technique is alluded to in two or three places in the text book but is not compared and contrasted appropriately in the preliminary discussion of techniques that are available and valuable in the diagnosis of early carcinoma of the lung. Also omitted from discussion is the x-ray evaluation of a given nodule newly discovered and known to be growing in size. In such single lesions most thoracic surgeons, having ruled out primary malignancy elsewhere in the body, would proceed with open surgical biopsy and removal, with a well over 90 percent degree of accuracy and avoiding other available but unnecessary diagnostic procedures. We are all concerned today with over-utilization of hospital bed space, x-ray facilities, laboratory facilities, and so on. The judgment of an experienced clinician in the selection of diagnostic procedures is of pragmatic importance.

The reviewer feels that the technique of trans-bronchial biopsy as so beautifully presented and illustrated fills a real need in selected cases; not in those where there is an isolated nodule of significant size that can either be biopsied by needle aspiration or by open thoracotomy, but in those cases where there is a positive cytology, or a segmental bronchial obstruction and yet no significantly sized nodule can be identified for the simpler methods of biopsy.

BEATTY H. RAMSAY, M.D.

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CONCEPTS OF DISEASE—Edited by Joel G. Brunson, M.D., Professor and Chairman, Department of Pathology, University of Mississippi School of Medicine; and Edward A. Gall, M.D., Professor of Pathology, Vice President and Director, University of Cincinnati Medical Center. The Macmillan Company, 866 Third Avenue, New York City (10022), 1971. 1134 pages, $23.95.

This book is designed for students of medicine. The editors have suggested that clinicians may be interested in this approach to the study of disease which, stated simply, is an attempt to single out the important basic elements of disease in cells and tissues and the use of details as illustrative material. It is suggested that this will prevent obscuring of concepts of disease by the vast body of detailed information concerning cells and their behavior that has become available in recent years.

Thirty-eight authors have contributed to the text. Probably in part because of this multiple authorship, the realization of the expressed goals has been achieved with varying success. There are still many details enumerated without any clear relationship to concepts. The book, however, is a serious effort to represent pathology in terms of the contributions of modern science without losing the heritage of this discipline. Electron micrographs, for example, are used liberally to illustrate ultrastructural changes in disease but these do not constitute a separate approach; they build upon knowledge that has been accumulated in other ways. A sharp separation of general and special pathology has been avoided, but several chapters compare differences in inflammatory reactions, cell functions and growth disturbances in different organ systems.

The book offers a helpful medium for viewing pathology in the context of present-day knowledge of biological science.

Alvin J. Cox, m.d.

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TREATING THE TREATMENT FAILURES—The Challenge of Chronic Schizophrenia—Arnold M. Ludwig, M.D., Professor and Chairman, Department of Psychiatry, University of Kentucky College of Medicine, Lexington, Ky. Grune & Stratton, Inc., 757 Third Avenue, New York City (10017), 1971. 235 pages, $12.00.

Dr. Arnold Ludwig has been interested over a long span of time in the treatment of chronic, treatment-refractory schizophrenic patients. Although, as Dr. Ludwig acknowledges, much of the data from this book has already been published, he justifies a book now because he wants to "summarize" his overall impressions on this particular subsample. He directs it to "clinicians charged with the care and treatment of these kinds of patients. Because they are obliged to act, to do something in the present, and cannot put these patients on 'ice' indefinitely until researchers come up with definitive answers to the etiology and therapy of chronic schizophrenia, clinicians require some practical guidelines and principles, at least on an operational basis, for therapeutic action."

The book contains a mixture of philosophy (for example, on treatment of schizophrenia, chronicity of schizophrenia, etc.), impressions (for example, attitudes of staff working with chronic patients and the discouragement they feel) and some helpful, practical "how-to-do-it" notions about management.

In addition, four experiments designed to modify schizophrenic symptomatology *without the use of medication* are presented. The first used small-group interaction as a lever for increased functional behavior. It failed. The second used a "buddy system" to change behavior and was successful. The third used a "double conditioning technique" to operantly condition some chronic schizophrenics to become operant conditioners ("the therapist-patients") of other chronic schizophrenics ("the patient-patients"). Results indicated that "therapist-patients" did better than "patient-patients." Finally, an experimental treatment program comparing "nonspecific influences," usually lumped under the term "milieu therapy," was compared to a control program for a week. There was significantly greater improvement in the experimental group than in the control.

Finally, there is a discussion of aftercare and its crucial importance in posthospital outcome.

What Dr. Ludwig has done—and it is no small accomplishment—is to show that inpatients with chronic schizophrenia who have not responded to other modalities can improve with various nondrug-related strategies while in the hospital. Whether or not they can maintain improvement within the community (and if so, for how long) is another question. But this is not the point of his work.

I think this book would be useful (not mandatory—but it's nice to know others are struggling with similar problems) to professionals working with psychiatric inpatients (regardless of diagnosis) or working with chronic schizophrenic outpatients using nonpsychopharmacologic methods.

There is an index and a not too complete bibliography. For example, the studies by May and those by Grinspoon, Ewalt and Shader have not been included. Their work with schizophrenics, comparing the relative efficacy of both drug and nondrug treatment strategies, in my opinion, bear directly on the issues Dr. Ludwig discusses.

Ref.: May P: Treatment of Schizophrenia: A Comparative Study of Five Treatment Methods, New York, Science House, 1968

Grinspoon L, Ewalt J, Shader R: Psychotherapy and pharmacotherapy in chronic schizophrenia. Am J Psychiat 12: 1645-1652, 1968

Ira D. Glick, m.d.

* * *

SHANDS' HANDBOOK OF ORTHOPAEDIC SURGERY—Eighth Edition—R. Beverly Raney, Sr., M.D., Clinical Professor of Orthopaedic Surgery and Chairman Emeritus of Division of Orthopaedic Surgery University of North Carolina School of Medicine and North Carolina Memorial Hospital, Chapel Hill, N.C.; H. Robert Brashear, Jr., M.D., Professor of Orthopaedic Surgery, University of North Carolina School of Medicine; Attending Orthopaedic Surgeon, North Carolina Memorial Hospital, Chapel Hill, N.C.; With the collaboration of Alfred R. Shands, Jr., M.D., Medical Director Emeritus, Alfred I. duPont Institute of the Nemours Foundation, Wilmington, Del.; Visiting Professor of Orthopaedic Surgery (Emeritus), University of Pennsylvania School of Medicine, Philadelphia. The C. V. Mosby Company, 3301 Washington Blvd., St. Louis, Mo. (63103), 1971. 543 pages with 419 illustrations and a bibliography of 1466 titles, $15.50.

This is an introductory textbook of orthopedics which is appropriate for medical students, interns and those who are receiving exposure to orthopedics for the first time. It is a newly revised edition of a long established textbook which has served medical students well for many years. The authors are well recognized authorities in the field who write lucidly and concisely. The book has been updated in numerous chapters where there have been recent advances in diagnosis and treatment of the musculoskeletal system.

Wayne H. Akeson, m.d.

* * *

PSORIASIS—Proceedings of the International Symposium, Stanford University, 1971—Edited by Eugene M. Farber, M.D., Professor of Dermatology, Stanford University; Alvin J. Cox, M.D., Professor of Pathology in Dermatology, Stanford University. Stanford University Press, Stanford, Ca. (94305), 1971, 478 pages, $18.50

This book contains over fifty manuscripts which were assembled by Drs. Farber and Cox after they were presented to the International Symposium on Psoriasis held at Stanford University in 1971.

The subject matter is broad in coverage and reasonably up-to-date. The book represents the many areas of interest in this disease and effectively brings them all together so that one can obtain a comprehensive picture of current concepts in this disease. It should serve as an excellent reference book for those people who are actively interested in this field or seek special information about this disease.

Richard B. Stoughton, m.d.

LEPROSY IN FIVE YOUNG MEN—George J. Hill, II, M.D., Assistant Professor of Surgery, University of Colorado School of Medicine, Denver; formerly Clinical Associate, National Institutes of Health, Bethesda, Maryland. Colorado Associated University Press, 1424 15th Street, University of Colorado, Boulder, Colorado (80302), 1971. 204 pages, $8.00.

This book is the result of an ambitious project initiated in 1962 by the National Institutes of Health, "to study the natural history of leprosy". Five male, Mexican nationalists from different parts of Mexico were brought to the United States for these studies. Four suffered from lepromatous leprosy and one from dimorphus leprosy. The entire admission consisted of two study periods—Study Period 1, for observation and medical tests, which lasted for two to three months, and Study Period II, lasting from three to seven months, during which period therapy was given.

The contents are arranged in three main parts, namely, case summaries, a discussion of the findings, and tables. The patients were given the most thorough clinical and extensive laboratory examination possibly ever carried out anywhere. Forty-one associate investigators are listed. The case summaries contain clinical photographs, occasionally including family members, and depicting living conditions, as an interesting sidelight.

The numerous photomicrographs vary greatly in quality. To demonstrate M. leprae in black and white is always disappointing.

The discussion of the abnormalities covers seven major areas of research; namely, skin and neuromuscular, bacteriology and pathology, immunology, ophthalmology, hematology, gastro-intestinal and adrenal-genito-urinary. The presence of lepra bacilli in practically all organs examined, including prostate and jejunum is stressed. One organ not mentioned where lepra bacilli have been demonstrated, is the tooth.

The fifteen tables contain, in concentrated form, the results of the investigation. Covered are, among others: abnormalities of the skin, neuromuscular abnormalities, mean density of the acid fast bacilli in hundreds of specimen, the results of 10 different skin tests, the results of 19 serological tests, serum proteins, hemological abnormalities, gastro-intestinal and hepatic functions, abnormalities in renal function, urinary cortico-steroid excretion, plasma cortico-steroid values, reproductive function, and innumerable additional laboratory studies.

The author was, at the time of these studies (1962-63), Clinical Associate at the National Institutes of Health, but stresses that the book is not an official publication of the U.S. Public Health Service. Apparently, no official publication from the National Institutes of Health about these studies has appeared. One of the reasons might be that although it contains a wealth of material, no new findings were presented.

The author does not explain how the length of Study Period I, during which specific therapy was withheld, was justified, even if the patients volunteered.

Paul Fasal, M.D.

* * *

CECIL-LOEB TEXTBOOK OF MEDICINE—Thirteenth Edition—Edited by Paul B. Beeson, M.D., Nuffield Professor of Clinical Medicine, University of Oxford; and Walsh McDermott, M.D., Livingston Farrand Professor of Public Health, Cornell University Medical College, with 1969 Contributors. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105) 1971. 1974 pages, 198 illustrations: Single Volume, $26.00, two-volume set $30.00.

The number of pages of this encyclopedic Textbook of Medicine has grown to 1923 exclusive of the index. In addition to two editors it has five associate editors as well as a total of 170 contributors of articles. Along with its growth numerically it has its usual good up-to-date coverage of diseases, their etiology, pathology, pathophysiology, diagnosis and therapy.

The book will probably be of most use to students and recent medical graduates. It is laid out for them as well as a one-volume encyclopedic reference can be. However, since the half life of medical information is probably less than seven years, many doctors of medicine whose entire scientific training took place before 1950 will find some sections difficult reading. The details of molecular biology can be rough going when authors assume that their readers are conversant with all the elementary principles involved. Incidentally, abbreviations should not be used in any section unless the meaning is written out in full previously in that section.

The last (or 12th edition) featured the introduction of two companion volumes on Roentgenologic Diagnosis as well as the renewal and expansion of the textbook proper. The present edition likewise contain much new material. One major section on "Respiratory Disease" is wholly new. However, the reviewer was unable to find normal values for blood gases, lung volume, mechanics of breathing or blood-gas distribution either in this section or in the tables of Normal Laboratory Values of Clinical Importance at the back of the book. The section on "Granulomatous Disease of Unproved Etiology" has been beefed up by the addition of several syndromes formerly classified under Diseases of Connective Tissue because of what one of the editors terms "the present state of ignorance" regarding their etiology. One of these, Polymyalgia Rheumatica, until recently only reluctantly classified as a disease, has been given three times the space it had in the last edition (while the putatively related Cranial Arteritis received only half the write-up it had before).

In this edition the editors demonstrate that they are aware of what is going on in the world around and beyond the individual patient. Dr. McDermott introduces the book with an essay on Medicine in Modern Society suggesting that the coincidence of massive scientific innovation and wide social change has created problems not solvable by good scientific personal medical practice alone. He offers no solutions except that we not avoid the emerging problem.

The reviewer was impressed by the reorganized and expanded section on Environmental Factors in Disease (increased from 22 to 60 pages and transferred from the back to the front of the book) and particularly by the encompassing introduction on Man in His Environment by Harold E. Lewis. This cogent article points out that a large part of the practice of medicine is devoted to treating human disorders which are expressions of inadequate or inappropriate responses to environmental influences. We need to know much more about man's environment as he faces the reality of daily life, and we need to know what effect our activities have on our environment.

Environmental knowledge has never been considered as a feature of medical education. The physician and the ecologist are both devoted to the welfare of a species but the former's primary concern has been for the individual while the latter deals with populations. Their differing philosophies may be noted in the assessment of a pesticide. The medical man is prepared to accept the results of acute or chronic toxicity tests and will be particularly concerned when individuals receive fatal doses. The ecologist is more anxious to assess the situation in terms of the biosphere.

Lewis suggests there is a feeling of helplessness against the demands of the technologic system which man has created but neither understands or effectively controls. The problem is not that of nature threatened by man, but of nature and man equally threatened by the uncontrolled working of technology. Physical or chemical crucial decisions need to be made concerning the consumption of fossil fuels and the production of nuclear energy, the accumulation of human waste, excessive air and water pollution, the effect of noise and the human population crisis. We have mishandled our technologic capabilities. How to strike the right balance may be the greatest challenge of human wisdom.

In summary, as we have before, we recommend strongly this one volume encyclopedic textbook of medicine.

EDGAR WAYBURN, M.D.

* * *

TRAUMA TO THE LIVER—2nd Edition (Volume III in the Series MAJOR PROBLEMS IN CLINICAL SURGERY—J. Englebert Dunphy, M.D., Professor and Chairman, Department of Surgery, University of California, San Francisco, Consulting Editor)—Gordon F. Madding, M.D. M.S. (Surgery), F.A.C.S., Associate Clinical Professor of Surgery, University of California San Francisco, Associate in Surgery, Stanford University School of Medicine; and Paul A. Kennedy, M.D., F.A.C.S., Assistant Clinical Professor of Surgery, Stanford University School of Medicine. W. B. Saunders Company, West Washington Square, Philadelphia, Pa. (19105), 1971. 186 pages, $9.50.

This concise coverage of a difficult clinical problem is eminently readable. Progressing from an overview of the historical developments in management of hepatic trauma the book goes on to detailed discussions of the most vital areas in the management of liver injuries today.

Excellent drawings, corrosion cast photographs and a color plate illustrate the anatomy of the bile ducts and vascular supply to the liver. The chapter on preoperative diagnosis and preparation of the trauma patient is covered adequately and touches briefly on associated injuries and their diagnosis. Controversial areas in hepatic surgery such as extrahepatic biliary drainage, intraperitoneal antibiotics, packing of liver wounds and even wound closure techniques are discussed fairly. The authors give reasons for their preferences. Especially helpful to the surgeon who deals with this type of injury infrequently will be the good coverage of complications attendant on liver injuries and their treatment.

The chapters covering techniques of liver resection by Blaisdell and Lim and repairs of injuries involving the hepatic veins, intrahepatic vena cava and/or the portal vein by McClelland, Canizaro and Shires are extremely well done and add the depth and breadth necessary to make this monograph one of extended value to those surgeons, practicing or training, who deal with a larger volume of liver injuries in metropolitan hospital areas.

In its clear and experienced coverage of the varied aspects of liver trauma the book serves as a valuable guide. To their credit, the authors have kept it well-edited and short so that it may be used as a refresher at the time of most need—when one is faced with urgent operative therapy of the patient with hepatic injury.

RONALD K. TOMPKINS, M.D.

* * *

THE MERCK MANUAL OF DIAGNOSIS AND THERAPY—12th Edition—David H. Holvey, M.D., Editor; John H. Talbott, M.D., Consulting Editor; Members of the Editorial Board: Elmer Albert, M.D., Philip K. Bondy, M.D., Edward J. Huth, M.D., Chester S. Keefer, M.D., Allen M. Kratz, Pharm.D., Dickinson W. Richards, M.D., W. Henry Sebrell, M.D., and Louis G. Welt, M.D. Merck, Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc, Rahway, N.J. (07065), 1972. 1964 Pages, $8.00, regular binding; $10.40, deluxe binding, and $6.40 for students, nurses, residents and interns.

The Twelfth Edition of the Merck Manual has come to hand. This new edition of an unexcelled resource for the medical student, the intern and resident in particular, and any practicing physician who may be in need of a quick and ready reference to diagnosis and treatment bids well to follow in the successful footsteps of its recent predecessors. It is well indexed and almost everything seems to be covered. The use throughout of the generic names for pharmaceuticals is to be commended, but may prove to be something of a hurdle for those who are unfamiliar with the tongue twisting and brain befuddling appellations which are more the lingo of the organic chemist than of the clinician.

M.S.M. WATTS, M.D.

* * *

TRIUMPH OVER PAIN—The Story of Anaesthesia—Robert H. Curtis, M.D. David McKay Company, Inc. 750 Third Ave., New York City (10017), 1972, 134 pages, $4.95.

"Pain is the enemy of the surgeon, and it was a great day for him and a better one for all of us when pain could be controlled."

The author follows through on this thought with a fascinating little book which highlights the story of anaesthesiology. Dr. Curtis has not only written an authoritative and enlightening book for everyone, but he has made it enjoyable and easy reading, i.e., painless.

Starting from earliest times, man sought relief from pain by using blows on the head, or the strong arms of attendants, or acupuncture, alcohol, and, finally, chemicals. The story is elaborated on the sporadic but consistent search for pain relieving remedies. The author deftly and succinctly gives us the story of the conquest of pain.

Aside from alcohol in the form of wine and the unpredictable use of morphine and hemp, there was a long lapse of several centuries while the science of chemistry was evolving before the precursors of modern anaesthetics were tried. The story of the trials and tribulations of the men involved in the development of ether, chloroform and nitrous oxide is intriguing.

This book is for all—layman, scientist, young and old. It doesn't take long to read, primarily because it is so well written that the reader wants to finish it. Here is a book that you will pass on to family and friends, and physicians will include it in their library for use by patients.

ROBERTA F. FENLON, M.D.

* * *

PROGRESS IN NEUROLOGY AND PSYCHIATRY—An Annual Review—Volume XXVI—Edited by E. A. Spiegel, M.D., Dr. Med. (Hon.), Emeritus Professor and Head of the Department of Experimental Neurology, Temple University School of Medicine, Philadelphia. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1971. 597 pages, $29.75.

This volume, like the 25 preceding annual volumes, is essentially an annotated bibliography. Each of the 28 chapters deals with a special aspect in the fields of neuroscience, neurology, neurosurgery and psychiatry. Such subspecialty areas as otoneurology, epilepsy, pediatric neurology, child psychiatry, alcoholism and peripheral nerve surgery are taken up. Each chapter is brief and is composed of a long series of simple declarative sentences each of which gives the gist of a specific article. These sentences are strung together in groups dealing with the same subject, without further discussion or editorial comment. Often, the bibliographies at the end of chapters are as long as the chapters themselves. The papers cited are primarily from the years 1969 and 1970, and the literature review is comprehensive.

In brief, this volume, like the others in the series, serves as a resource for pursuing the current literature in the field of neurology and psychiatry. It is a useful guide to aid the student, resident or specialist in finding recent pertinent articles. It is recommended for neurology and psychiatry departmental and institutional libraries, and for the specialists in these fields.

ARTHUR K. ASBURY, M.D.

PEDIATRIC CLINICAL GASTROENTEROLOGY—Arnold Silverman, M.D., Director of Graduate Education and Head of Pediatric Gastroenterology Service, The Children's Hospital, Associate Clinical Professor of Pediatrics, University of Colorado Medical Center, Denver; Claude C. Roy, M.D., Professor of Pediatrics, Hospital Sainte Justine and University of Montreal, Montreal, formerly Associate Professor of Pediatrics, University of Colorado Medical Center, Denver; and Frank J. Cozzetto, M.D., Associate Professor of Pediatrics, University of Colorado Medical Center, formerly Medical Director, The Children's Hospital, Denver. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. (63141), 1971. 580 pages, $39.50.

The authors intended this book to "bridge the gap" between relatively brief discussions of gastroenterology in standard pediatric textbooks and the complete standard textbooks of gastroenterology. They have succeeded. Knowledge in the field of pediatric gastroenterology has expanded suffiently in the past two decades to make this a worthwhile and necessary undertaking.

The book is divided into three parts, the first dealing with "Common Gastroenterologic Symptoms and Signs," the second with "Disease Entities" and the third with "Laboratory Tests and Procedures and Nutritional Aspects." In the first part, some 45 pages are devoted to a very good correlation between symptoms and etiology. In the second part, 25 diseases are discussed in detail. These range from gastrointestinal emergencies of the neonate to pancreatitis and include particulary good discussions of disaccharide intolerance, protein-losing enteropathy, liver disease and cystic fibrosis of the pancreas. In the third portion, tests for liver and pancreatic function, absorption, etc. are clearly presented.

Many tables add to the value of the book. The tables, such as the one on page 26 outlining "clinical clues to causes of rectal bleeding" and that on page 251 listing "elective defects of absorption," will be found to be particularly helpful to the clinician. Unfortunately, the quality of reproduction of histologic sections and of the x-rays leaves a great deal to be desired. The numerous diagrams, however, are excellent.

Pertinent selected references, although few in number, may be found at the end of each chapter.

The authors worked together in the Department of Pediatrics at the University of Colorado Medical Center, and their close collaboration has resulted in a readable contribution. Although there are minor points with which one might differ and which detract, the book nevertheless represents the most complete and best text available on the subject in the English language, and can be recommended. The price, unfortunately, is high for a book of only 562 pages—$39.50. Perhaps this is due to the numerous illustrations.

BENJAMIN M. KAGAN, M.D.

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PROGRESS IN ATOMIC MEDICINE—Volume 3—Recent Advances in Nuclear Medicine—Edited by John H. Lawrence, M.D., D.SC., Donner Laboratory and Donner Pavilion, Lawrence Radiation Laboratory, University of California, Berkeley. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1971. 246 pages, $15.00.

This volume contains seven chapters, contributed by 20 authors. Fourteen of the authors are from the Donner Laboratory and Donner Pavilion, Lawrence Radiation Laboratory, University of California, Berkeley.

Excellent articles and the experience resulting from investigations at this institution are presented in chapters on the following subjects: "Potential early diagnosis of cancer with radioactive compounds"; "Trace elements in biology and medicine"; "Some considerations of physical and biological factors in radiotherapy with high-let radiations including heavy particles, pi mesons, and fast neutrons"; and "Heavy-particle therapy for acromegaly, Cushing's disease, Nelson's syndrome, and nonfunctioning pituitary adenomas."

There is an excellent chapter on the "Present status of radioiodine therapy on thyroid disease" by W. H. Beierwalter. This chapter presents data from the national study as well as the experience gained at the University of Michigan over a period of years.

Saenger and Kereiakes at the University of Cincinnati College of Medicine summarize current attitudes regarding investigation in human subjects and the essential aspects to the determination of safe tracer doses. Acceptable rules for procedures using radioactive compounds in human research, guides for calculation of doses, and doses for infants and children are discussed in adequate detail.

John S. Laughlin and associates from Sloan-Kettering Institute for Cancer Research, New York, have a chapter on "The cyclotron: Source of short-lived radionuclides and positron emitters for medicine." The history of the development of the cyclotron and cyclotron produced radionuclides in medical cyclotrons is discussed. The authors anticipate the greater use of the cyclotron for medical research and diagnosis with respect to the development of high yield reactions for specific nuclides, labelling of biologically significant compounds, and analytical methods for short-lived nuclides.

This volume would be a worthwhile addition to the library of any physician or physicist interested in the medical aspects of nuclear energy from either the clinical or research standpoint.

JUSTIN J. STEIN, M.D.

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INSTRUCTIONAL COURSE LECTURES—Volume XX, 1971—The American Academy of Orthopaedic Surgeons. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. (63141), 1971. 244 pages, $20.00.

Instructional Course Lectures, Volume XX, 1971 is a series of unrelated articles on orthopedic topics reviewing material both new and old by people knowledgeable about the topic. This is an ongoing series published yearly. This volume contains twelve articles.

The first article on orthopedic infections gives a good basic review of the biology and physiology of bacteria in bone and the clinical significance of osteomyelitis. The major point is that the bacteria must be identified for proper treatment. There is little new in this article.

The second article deals with the orthopedic management of hemophilia. The importance of the use of cryoprecipitated and glycine precipitated factors from blood plasma is stressed. A method of treating acute bleeding in joints is described. Treatment of long term deformities in the musculoskeletal system secondary to hemophilia is briefly discussed.

The third article is a discussion by four different experts on cerebral palsy in the lower extremity. The recognition of problems is stressed. This article is useful to all people dealing with cerebral palsy by stressing the recognition by physical diagnosis of problems in the lower extremity.

The fourth article discusses the painful shoulder listing the entities one must consider particularly as defined on the basis of physical examination. This constitutes a good review article.

Fractures of the shafts and distal ends of the radius and ulna is an excellent and current discussion of treatment, providing knowledge on the use of both rods and plates and particularly where each is most valuable.

The sixth article on lower extremity bracing by four different authors is difficult to read. It discusses gait and alignment of lower extremity from an orthotic point of view. The last section of this article is an exhaustive description of appliances and their application to specific problems with no relationship to diagnosis. A useful but difficult article.

The next three articles are on advanced degenerative arthritis of the hip by four authors and the next two by a single author give a good clear and timely discussion of methods of treatment of osteoarthritis of the hip. Particularly it defined the different operations that exist and their usefulness and relationship to one another. I think for general reading this is the most useful series of articles in the volume.

The tenth article on surgical anatomy and exposure of the knee joint is too superficial to be of value.

The eleventh article is a timely discussion of osteoarthritis of the knee. It is based on the author's book on the subject and best serves as an introduction to that volume.

The last article is an excellent and exact discussion of synovial fluid analysis and is useful to all physicians dealing with patients. Next to the articles on degenerative arthritis of the hip, I would feel this is the most useful article in this volume particularly for general reading.

J. Paul Harvey, Jr., m.d.

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DEALING WITH DRUG ABUSE—A Report to the Ford Foundation—Foreword by McGeorge Bundy—The Drug Abuse Survey Project—Patricia M. Wald & Peter Barton Hutt, Co-chairmen; James V. DeLong, Executive Director; Edgar May, Annette Abrams, Peter A. Wilson, Peter B. Goldberg, John F. Holahan, Paul A. Henningsen and Andrew T. Weil, M.D. Praeger Publishers, 111 Fourth Avenue, New York City (10003), 1972. 396 pages, $8.95.

I must confess that when I was asked to review the volume "Dealing with Drug Abuse—A Report to the Ford Foundation" my reaction was one of initial dismay, for I had already read the volume and had a number of reservations about it. However, a review for a medical journal obviates some of this reluctance. My hesitations have to do, not so much with the survey project or the staff papers themselves, for all the words are there, but rather the "music" is lacking; namely the "gut level" expertise behind the words. It is obvious that the staffers worked hard and long in interviewing people in the drug field and attended multiple drug conferences, but it is equally obvious that they have had very little grassroots experience in working with the drug abuse problem. So, while the report covers a wide range of the drug problems in many areas it misses many, if not most, of the essential ingredients for a significant contribution.

It is as though a medical student were writing a review paper for a journal or a Ph.D. were writing his thesis, each about some rather exotic, rarely-seen syndrome where a review of the literature would be necessary. However, when we talk about drug abuse, we are dealing with the third most pressing problem of concern to the American public (according to the National drug commission's recent national survey), a problem which is just behind that of Vietnam (and gaining on it) and behind the number one issue, the economy.

Thus for the practicing physician who is working with drug abusing patients, there is little here that is not contained in dozens of other volumes. For the retired physician, at home, who merely wishes philosophical discussion about heroin maintenance, altered states of consciousness, or about theories of various mechanisms of action of some of the opiates, etc., this may provide some intellectual relief. But we really are in a time of crisis and deep concern about drugs and nowhere does the volume present or pinpoint this. Perhaps the most surprising thing is that the staff report was not kept within the Ford Foundation but was released and published (as is almost anything that is written about drugs today) for general distribution to the public. But this is a time when the drug problem has become politicized and is now being institutionalized and it is a time when the control/enforcement, prevention/education, and treatment/rehabilitation forces are all seeking funding and emphasizing their modalities, each as top priority items. This book sheds little light on how such priorities might accurately be ascertained.

In an analogous fashion many had hoped that when President Nixon created the new SAODAP (Special Action Office for Drug Abuse Prevention) the drug politicization process would diminish. This office was to "tell things like they are" and if necessary "heads would roll." But unfortunately, that proved to be just another myth; even there no one dares to reveal the boondoggling, vested interests and downright incompetence which is so obvious in so many of the governmental agencies dealing with drug abuse. Even those "civilian professionals" who were selected for this office and had previously been critical and honestly outspoken have now remained curiously silent on many of the pressing drug issues of the day (for example, repeated "no comment" on the National Commission on Marijuana and Drug Abuse's recommendations made to the President and Congress this March).

Thus, many people were looking to the Ford Foundation and subsequently their privately funded drug abuse consortium that developed as a sophisticated form of (Ralph) "Nader's Raiders," who could and would "tell it like it is" and would reveal that the same problems are happening in drugs that happened in the poverty program (with the patients being disregarded, as others vie for political and financial power under the rubric of "drug abuse program"). This report alludes to all kinds of problems, but doesn't specify which ones deserve top priority, and apparently is suffering from an institutionalization process of its own. Perhaps it is necessary (for a Foundation, with a Board of Directors, who exert policy control) to "not rock the boat," especially when the group is based in Washington. Certainly this has been true for the advertising of anti-drug commercials, as lobbying groups protested certain anti-drug advertisements until the final result was a watered down, probably ineffectual product. At any rate, it looks very much from the subsequent press releases of the Ford group, as the consortium was formed, that they based their goals on this volume and that we will now have just another similar "government-type agency."

But there is a definite need for a critical evaluation of drug programs, as huge amounts of money are being wasted and there is a tragic lack of patient care and long waiting lists for urgent priority items like methadone maintenance and half-way house treatment. The tragic dichotomy between law enforcement and medicine continues, with medicine having abrogated its responsibility for treatment, with young experimenters sometimes winding up in jail while major pushers go free, and with the padding of law enforcement "felony arrest" statistics (that is, for marijuana possession) continues. But nowhere does anyone come forward to challenge this. I am pessimistic in general, and especially from this volume, that the Ford Foundation and consortium will cause anything constructive to happen in this area of most dire need. If this seems like an unduly pessimistic review of this report perhaps it is only a reflection of the reviewer's personal bias, although I must say that several other professionals with whom I have checked have had the same reaction to the volume and the initial excitement that once greeted the idea of the consortium has faded as it has yet (if ever) to even begin to approach fruition.

J. Thomas Ungerleider, m.d.

Refer to: McConnell RY, Fox RT: Experience with percutaneous internal jugular-innominate vein catheterization. Calif Med 117:1-6, Aug 1972

California Medicine
THE WESTERN JOURNAL OF MEDICINE

Experience with Percutaneous Internal Jugular-Innominate Vein Catheterization

Richard Y. McConnell, m.d., *Tokyo*, and
Robert T. Fox, m.d., *Long Beach*

■ *A specific technique of cannulation of the internal jugular innominate vein, presented herein, is not considered an innocuous procedure, but the incidence of serious complications is very low. In this technique a needle-in-catheter unit aids greatly in advancing the catheter through the vein. More than 62 percent of the catheters were left in place for more than five days. There was an 11.4 percent incidence of positive bacterial or fungal cultures from the catheter tip. Routine follow-up chest x-ray films demonstrated all the catheters in the innominate-superior vena cava venous system.*

In the aggressive and successful management of seriously ill surgical and medical patients, central venous cannulation is often indicated.[1-8] In each of the "indications" requiring fluid replacement, the central venous pressure may be monitored serially, thus insuring adequate volume replacement without over-loading.[9-12] Therefore, a number of techniques for placement of a catheter in the central venous system have been described and reviewed in the past.[12-18]

With the growing interest and recognition of the usefulness of central venous pressure (CVP) monitoring, a reliable technique of placing a catheter tip near or in the right atrium is now both useful and important.[1,3,16] The indications for measurement of the CVP have been well elaborated and the interpretation of serial readings discussed in detail.[19-24]

This paper reviews our experience with a specific technique of internal jugular-innominate vein cannulation.

Methods

During the nine-month period from August 1970 through April 1971, percutaneous internal jugular-innominate vein cannulation was performed 371 times on 357 seriously ill patients at the Memorial Hospital Medical Center of Long Beach, Long Beach, California. Of the total number of patients, 306 were on the surgical services and 51 on the medical services (Table 1).

All of the cannulation attempts included in the study series were carried out by one or the other of the authors. In this way there was guaranteed consistency in technique. In most cases catheterization was an elective procedure and sterile technique was employed. When the procedure was done in emergency, it was most often on patients in cardiopulmonary arrest.

Captain, USAF, MC, 475th USAF Dispensary, PACAF (McConnell); Assistant Clinical Professor in Surgery, University of California, Los Angeles (Fox).

From the Department of Surgery, Memorial Hospital Medical Center of Long Beach, and the Department of Surgery, Harbor General Hospital, Torrance.

Submitted, revised, November 2, 1971.

Reprint requests to: Robert T. Fox, M.D., 3490 Linden Avenue, Long Beach, Ca. 90807.

TABLE 1.—*Primary Indications for Central Venous Cannulation in 371 Procedures*

Indications	*Number*
Cardiopulmonary arrest	31
Parenteral hyperalimentation	43
Severe burns	1
Prior to major surgery in high-risk patients	11
Immediate post-operative cardiovascular instability	33
Acute circulatory failure, excluding patients in the first 24 hours post-op.	63
Unable to cannulate a peripheral vein or perform venipuncture	59
Severe oliguria or anuria	6
Massive fluid replacement	113
Phlebotomy	11
Total Catheterizations	371

Seventy consecutive patients (the 210th to the 279th) were studied to evaluate the infectious complications of this procedure. Cultures were obtained from the skin around the catheter and the distal 2 cm tip of the catheter. The skin was prepared with an iodine and alcohol preparation before the catheter was removed.

Seventy consecutive patients (catheterization 185th to 254th) were studied with chest radiographs following injection of a solution of 60 percent meglumine iothalamate (Conray®-60), a radiopaque dye, to delineate the contour and the extent of the catheter.[25]

Technique

In this approach to catheterization, the right side of the neck is preferred because the dome of the right lung is lower, there is a more or less straight line to the right atrium, and the thoracic duct is not in the way. The most important anatomical points to remember are that the internal jugular vein is anterolateral to the common carotid artery and "ends behind the medial edge of the clavicular head of the sternocleidomastoid muscle just above the medial end of the clavicle."[26,27]

The procedure is most easily performed with the patient supine and his feet elevated 15 to 20 degrees, or in a 15 to 20 degree Trendelenberg position. The patient's head is rotated only slightly to the left (hyper-rotation will distort the anatomy of the neck). The anterior neck between the mandible and the clavicle is cleansed with tinture of Zephirin® 1:750, and sterile towels are placed.

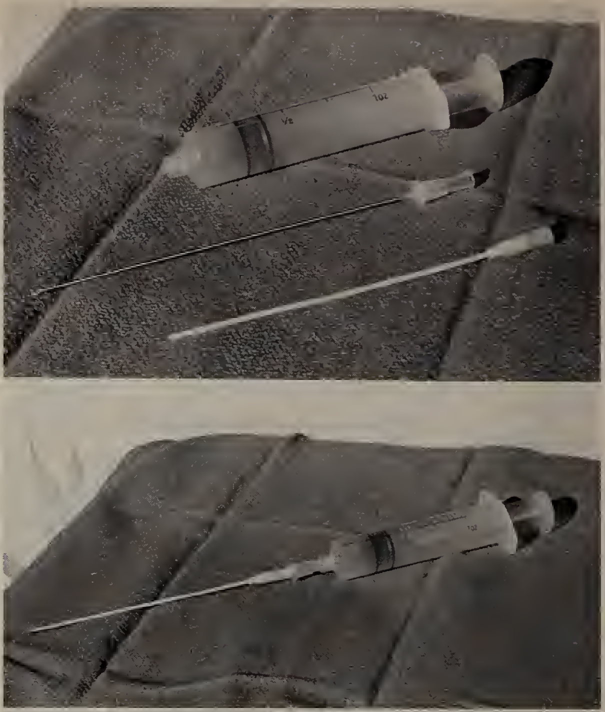

Figure 1.—*Above,* The Angiocath unit 14 gauge, 5¼ inches long) unassembled, and a large plastic syringe. *Below,* the unit assembled and attached to the plastic syringe ready for use.

The correct identification of the area of insertion is important to the success of this procedure. This point is located 4 cm above and 2 cm lateral to the suprasternal notch of Burns. This also locates the point of insertion in the apex of the triangle formed by the clavicle and the sternal and clavicular heads of the sternocleidomastoid muscle. A 25 gauge needle is used to infiltrate lidocaine (Xylocaine®) in the skin and the proposed needle tract.

We have used exclusively the 14 gauge, 5¼ inch Deseret Angiocath unit for the catheterization (Figure 1). Attaching a large plastic syringe (20 or 30 ml) with a luer tip to the needle-in-catheter unit provides better control of the needle, and the tight seal with the needle prevents air from entering the venous system during respiratory excursion. With the unit assembled as in Figure 1, the skin is penetrated and the needle is then carefully directed at an angle 35 to 40 degrees posterior to the coronal plane of the body and parallel to the saggital plane of the body (Figure 2). Next it is slowly advanced through the deep cervical fascia with negative pressure in the syringe. The needle is withdrawn to the skin surface should any of the following occur:

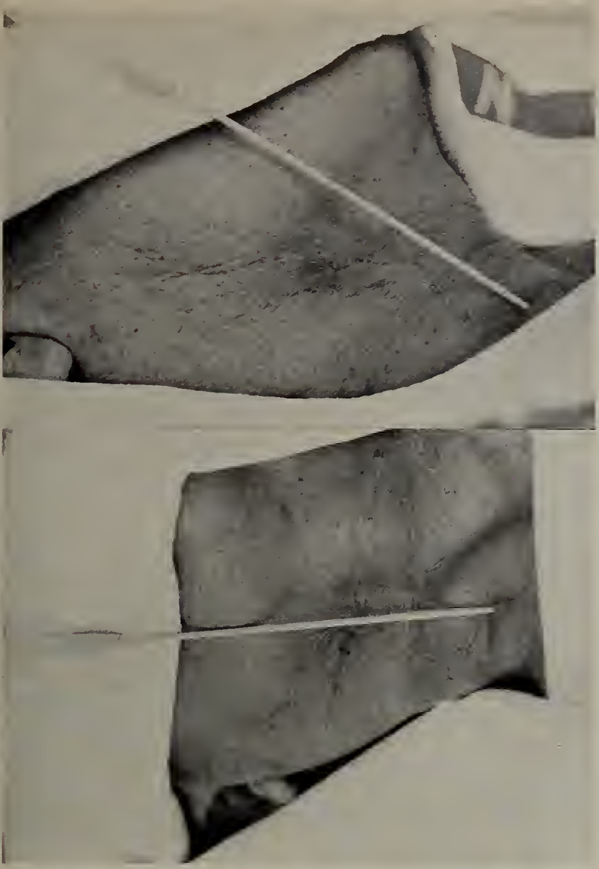

Figure 2.—*Above,* A lateral view of the right side of the neck, showing the needle-through-catheter unit 35 degrees to the coronal plane of the body. *Below,* a view from above the anterior neck region, with the needle-through-catheter unit parallel to the saggital plane of the body.

pulsation felt against the catheter tip or the return of bright red pulsatile blood; 2-inch advancement without blood return; aspiration of air; inability to advance the needle. During the second attempt at advancement, the tip of the needle should be directed 10 degrees laterally.

After the vein is penetrated, a free flow of blood will enter the syringe. Without changing the position of the needle, the catheter is advanced along the needle (Figure 3). Any difficulty in advancing the catheter is probably because it is lodged against the posterior wall of the vein. This can be alleviated by changing the previous 35 to 40 degree angle with the coronal plane to 10 to 15 degrees, and then proceeding with the advance. After the catheter has been advanced, the needle is removed and the syringe is attached to the catheter in order to recheck for blood return. Care must be taken to cover with the gloved finger the open end of the catheter when disconnected in order to prevent air embolus.[28] The catheter is then connected to tubing ready for infusion (Figure 4).

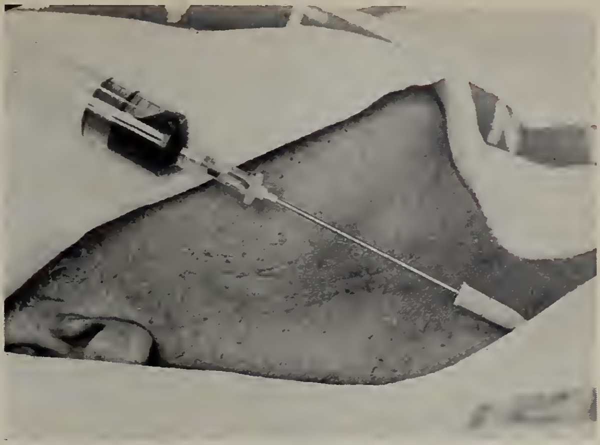

Figure 3.—Free aspiration of blood, and the catheter advanced along the needle.

The catheter is fixed to the skin at a point 2 cm from the insertion site with a No. 4-0 silk suture. A topical bacteriostatic agent as an ointment (Neosporin®) is applied locally and a small sterile dressing is placed over it and taped securely. The dressing is changed every other day and the bacteriostatic agent is reapplied at the time of change.

Results

This series demonstrates a variety of possible dangers inherent in percutaneous placement of an internal jugular vein catheter (Table 2). Pneumothorax occurred in four patients. In one patient a 50 to 60 percent tension type pneumothorax occurred and was treated with closed thoracotomy tube drainage without difficulty. In three patients simple pneumothorax of 15 percent or less was shown on x-ray films of the chest but the air resorbed spontaneously. Hydrothorax occurred in one patient in whom the catheter penetrated the posterior wall of the vein and fluid infused into the pleural space. Puncture of the common carotid occurred in eight patients, but application of 5 to 10 minutes of direct pressure stopped the bleeding. In an elderly patient with a tortuous, laterally displaced common carotid artery, puncture can be avoided by pressing the vessel with the middle and index fingers to displace it medically.[18]

In 23 percent of the patients in this series there were abnormal conditions that made cannulation by the technique we described less easy or caused

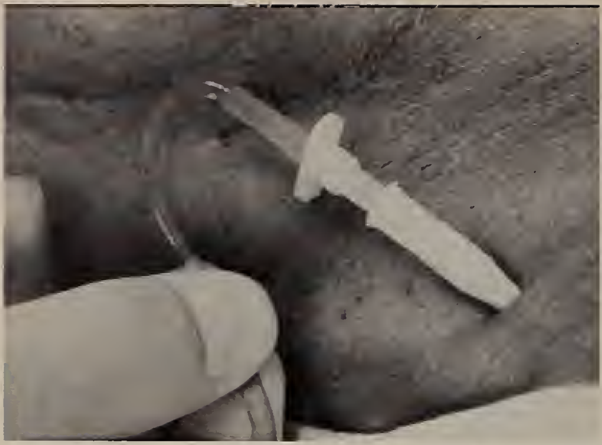

Figure 4.—The catheter advanced to the "hub" of the unit, the needle-core removed, and the tubing connected for infusion.

concern about the possibility of complications (Table 3). Four of the patients had had unilateral pneumonectomy in the past and in three others there was pre-existing pneumothorax. In these cases catheterization was successfully accomplished after radiological and physical examination to determine whether there was significant tracheal or mediastinal deviation. In 36 cases severe obesity (weight over 250 pounds in a man, over 200 pounds in a woman) obliterated certain landmarks of the two heads of the sternocleidomastoid muscle. Tracheostomy in nine patients not only distorted the surface anatomy but so limited the area for securing the dressing that the possibility of contamination and local infection was somewhat enhanced. Twenty-seven patients were receiving anticoagulant agents, but no significant subcutaneous or internal bleeding occurred. One patient with residual muscle atrophy of the right shoulder girdle and arm from poliomyelitis and a past history of a fractured clavicle had severe distortion of the anatomy of the area. It was in that case that the catheterization attempt resulted in the 50 to 60 percent pneumothorax mentioned above.

The catheters were left in place for a relatively long time—for periods of more than five days in 62 percent of cases, and in 6 percent for more than 21 days (Table 4).

Aerobic and anaerobic bacterial and fungal cultures of material from the catheter tip were obtained from 70 consecutive patients. They were positive for organisms in eight cases (Table 5). In those cases the average length of time the catheter was kept in place was 15.6 days, with a range of 4 to 32 days. In Cases 2, 4, and 5 (Table 5) the patients were receiving parenteral hyperalimentation. Candida albicans was cultured from all three. Only in Case 2 was the patient

TABLE 2.—*Complications Resulting from Internal Jugular Innominate Vein Cannulation (371 Catheterizations)*

Complications	*Number*
Pneumothorax	4
Hemothorax	0
Hydrothorax	1
Subcutaneous hematoma and/or infiltration	5
Mediastinal infiltration	0
Subcutaneous emphysema	0
Common carotid artery puncture	8
Brachial plexus injury	0
Catheter embolism	0
Air embolism	0
Cellulitis (local)	1
Septicemia	0
Severe phlebitis	0
Occlusion of jugular, subclavian, or innominate vein	0
TOTAL	19

TABLE 3.—*Hindering Circumstances Encountered (371 Catheterizations—357 Patients)*

Pre-existing pneumothorax	3
Previous pneumonectomy	4
Burns of the head and neck	1
Residual muscle atrophy (polio) and previous clavicular fracture	1
Anticoagulants	27
Tracheostomy	9
Severe obesity (men over 250 lbs., women over 200 lbs.)	36
TOTAL	81

TABLE 4.—*Length of Time Catheter Was Left in Place (Excluding 16 Unsuccessful Cardiopulmonary Resuscitations)*

Duration	*Number*	*Percent*
Less than 6 hours	4	1
6 to 24 hours	20	6
24 to 48 hours	10	3
48 to 72 hours	14	4
72 to 96 hours	26	7
96 to 120 hours	61	17
5 to 7 days	101	28
7 to 14 days	56	16
14 to 21 days	43	12
Over 21 days	20	6
TOTAL	355	100

TABLE 5.—*Results of Culture (70 Consecutive Patients)*

Case	*Organism*	*Catheter*	*Skin*	*Catheter in place (days)*	*Other Site Positive*
1	Klebsiella sp.	+	+	6	Tracheostomy
2	Candida albicans	+	+	32	Urine, blood
3	Enterobacter	+	−	4	Abdominal wound
4	Candida albicans	+	+	29	None
5	Candida albicans	+	+	18	None
6	Yeast (unidentified)	+	+	16	None
7	Staphylococcus albus	+	+	6	None
8	Staphylococcus aureus (+)	+	+	14	None

febrile, but the temperature returned to normal within 24 hours after removal of the catheter. In Case 3 the catheter was placed during cardiopulmonary arrest. Enterobacter organisms were cultured from both a surgical abdominal wound and the catheter tip but blood cultures were negative. In Cases 6, 7, and 8 the catheter was placed by sterile technique; none of the patients were febrile, and all the blood cultures were negative.

In the previously mentioned chest x-ray studies in 70 consecutive cases, none of the catheters was found to be extending into the ipsilateral subclavian vein or the contralateral innominate vein, or penetrating outside the vein or curling and kinking back upon itself.

Comment

Of the alternate methods of placing central venous catheters, Craig et al[16] found the subclavian route was the most successful, but studies by Yoffa,[2] Smith,[29] Matz,[30] and Schapira[31] called attention to multiple associated serious complications and failures. Bradley[32] considered the use of the saphenous vein or femoral vein inadvisable if there is any suggestion of thromboembolic disease, and Landis et al[33] discussed the complications of in-dwelling catheters in the inferior vena cava. We believe the internal jugular innominate vein technique is more dependable with fewer complications, but a specific routine, a knowledge and appreciation of the anatomy and an awareness of the possible complications are important. Bernard and Stahl[34] showed that complications from subclavian venipuncture are directly related to the experience of the person performing the procedure. But even with experience some complications, probably related to anatomical variations, are inevitable.

Bernard, Stahl, and Chase[35] very adequately reviewed the literature on the infectious complications of venous catheters. In their own series of subclavian catheterization, there was a 39.8 percent incidence of positive culture of the catheter tip.

In our series the incidence of positive cultures of the catheter tip was 11.4 percent. Cultures of Candida albicans were obtained from three of 17 patients (17.6 percent) who had been receiving parenteral hyperalimentation for an average of 26 days. Every two to three days the dressing was changed, the skin about the site of insertion was cleansed, and bacteriostatic antibiotic ointment was apparently applied aseptically. In each of the three cases the catheter acted as a nidus of infection of fungal organisms from the skin. This data supports the suggestion by Bernard et al[35] that a fungistatic agent be added to the antibiotic ointment.

Since high blood flow around the catheter favors long-term sterility, Wilmore and Dudrick[8] advocate the placement of catheters in large lumen central veins rather than in peripheral vessels.

The greatest advantages of the technique as described here are: The landmarks of the point and angle of insertion of the catheter are readily located; the catheter is advanced along the needle into the vein without need to disconnect the syringe; the strength of the catheter decreases the possibility of kinking and curling; the length of the catheter (5¼ inches) is such that it can be inserted up to its hub, thus eliminating guesswork as to how far to advance it; and "maintenance of long-term sterility is favored by high blood flow around the catheter."[8]

TRADE AND GENERIC NAMES OF DRUGS

Xylocaine® Hydrochloride	lidocaine hydrochloride
Neosporin® Ointment	polymyxin-bacitracin-neomycin
Conray®-60	meglumine iothalamate, 60%

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MECHANICAL VENTILATION IN OBSTRUCTIVE LUNG DISEASE

What are your indications for mechanical ventilation in patients with acute-on-chronic obstructive lung disease?

First of all, is the patient an emergency? Has the patient been allowed to go above 90 mm of mercury on uncontrolled oxygen therapy? If the PCO_2 is above 90 and you remove oxygen even for a very short time, the patient will die because his arterial oxygen will drop into that very low level. If the PCO_2 has been allowed to go very high, the patient obviously must be ventilated. On the other hand, if the patient has a PCO_2 which rises over the course of an hour or two to 80 or 90 mm of mercury on controlled oxygen and if at the same time he becomes more drowsy and unable to cough and if all our conservative measures of suction, physiotherapy, and general encouragement fail, then we put him on the ventilator.

Finally the third indication—if we have given the patient controlled oxygen therapy and failed to keep his PO_2 well above 30, then we may well consider ventilation at an earlier stage. But we would not ventilate any patient who was virtually confined to bed or confined to the house beween attacks. And we try and direct our attention to the patient who has some possibility of getting back to a useful existence after attacks.

—M. Keith Sykes, M.D., London
Extracted from *Audio-Digest Anesthesiology*, Vol. 13, No. 20, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

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Comparison of Carisoprodol, Butabarbital, and Placebo in Treatment of the Low Back Syndrome

THOMAS H. HINDLE, III, M.D., *La Palma*

■ *A double-blind study was carried out to determine the effectiveness of a muscle relaxant, carisoprodol, in the treatment of the low back syndrome, and to test whether this drug would produce any greater effect than an active sedative control. Forty-eight Mexican migrant farm laborers with acute lumbar strain and spasm were given either carisoprodol 350 mg, butabarbital 15 mg, or placebo, four times daily for four days, and then were rated on pertinent symptoms, the degree of limitation of motion (by an objective finger-to-floor test), and overall improvement. In the 43 patients who could be statistically analyzed, carisoprodol was shown to be significantly more effective than butabarbital or placebo in producing improvement of all factors rated. This result suggests that the effects of carisoprodol are not due solely to sedative action, but are also related to its muscle relaxant activity.*

THE ADJUNCTIVE USE OF MUSCLE RELAXANT drugs in the management of pain, spasm, and stiffness associated with musculoskeletal trauma has found wide support in clinical practice.[1-5] Notwithstanding this fact, the effectiveness of these agents, when given orally, has been questioned, and their benefits sometimes attributed simply to their sedative action.[6-7]

Since our practice serves a large number of migrant farm laborers whose work frequently produces acute lumbar strain, it appeared to offer a suitable clinical situation for conducing a controlled test of a muscle-relaxant drug.

The Study

A double-blind study was undertaken to evaluate the efficacy of carisoprodol Soma® in relieving pain and spasm in the "low back syndrome." Placebo was used as an inactive control and butabarbital 15 mg as an active sedative control. A higher dosage of butabarbital was not used because the resultant drowsiness might have broken the "blindness" of the study.

The Population

The subjects of this study were all Mexican braceros, contract laborers who cross the border into California to farm the crops of the Imperial Valley. Because of protracted stooping and carrying, the "low back syndrome," characterized by lumbar spasm and acute lumbar strain, is an occupational hazard in this population. Forty-eight patients with this condition entered the trial. Twenty-seven were men and 21 women, with ages ranging from 18 to 70 years (average 38.4). In 37 patients the onset of symptoms had occurred within the preceding 12 to 24 hours; in

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From Imperial General Hospital, El Centro.

Submitted July 8, 1971.

Reprint requests to: T. H. Hindle, III, M.D., 8032 Hummingbird Circle, La Palma, Ca. 90620.

TABLE 1.—*Time from Onset of Symptoms to Baseline Evaluation*

Time (Hours)	*Carisoprodol (N=16)*	*Butabarbital (N=16)*	*Placebo (N=16)*
0-12	1	3	2
12-24	14	11	12
24-48	1	2	2

TABLE 2.—*Demographic Distribution*

	Carisoprodol (N=16)		*Butabarbital (N=16)*		*Placebo (N=16)*		*All Treatments (N=48)*	
Age	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*
Under 20	—	—	—	2	—	—	—	2
20-30	4	3	2	2	2	1	8	6
31-40	2	2	5	1	3	3	10	6
41-50	1	1	—	3	1	2	2	6
51-60	1	—	1	—	1	—	3	—
61-70	1	1	—	—	3	—	4	1
Total	9	7	8	8	10	6	27	21
Average	37.0		34.6		43.5		38.4	
Median	35.0		36.0		38.0		37.0	
Range	21-66		18-52		24-70		18-70	

TABLE 3.—*Reasons for Dropouts at Various Stages of Trial of Muscle Relaxant Drug*

Medication	*Patient No.*	*Age*	*Sex*	*Onset (Hours)*	*Reason for Discontinuance*
Carisoprodol	42	21	M	0-12	Condition worsened. Patient sought another doctor after day 2 for pain medication.
	43	66	F	12-24	Patient refused to continue in study after initial visit. No evaluation possible.
Butabarbital	25	43	F	12-24	Dropped from study because of drowsiness first day on drug. No evaluation possible.
Placebo	21	30	M	12-24	Not seen after first visit. No evaluation possible.
	48	38	M	12-24	Condition worsened. Patient refused to continue after day 2.

six cases, within less than 12 hours; and in five, within 24 to 48 hours of initial treatment (Table 1).

Method

Patients were assigned sequentially, as they entered the study, in accordance with an allocation schedule derived from a table of random numbers.[8] (After completion of the trial, it was made known to the investigator that randomization had been carried out in groups of six, two patients per drug, in order to balance the treatment groups over time.) This assignment put 16 patients, comparable as to age and sex, into each drug group (Table 2). Five patients dropped out at various stages of the trial (Table 3). The loss of these five patients left 14 in the carisoprodol and placebo groups and 15 in the butabarbital group who completed the study. These treatment groups remained comparable for age, sex, and time of symptom onset.

Medications were provided* as identically appearing tablets of carisoprodol 350 mg, butabarbital sodium 15 mg, or placebo, each patient receiving the medication coded for his roster number, in bottles labelled to keep either the patient or the investigator from identifying the medication. The treatment in all cases consisted of one tablet of the assigned medication taken three times a day and at bedtime for four days. Specific medications for concomitant diseases were permitted, but these did not include sedatives, tranquilizers, or muscle relaxants. Patients remained off their jobs as long as pain continued.

Measurements and Rating Criteria

On first examination, and on days two and four after start of medication, the following ratings were recorded:

1. Evaluation by the investigator of the severity of the following symptoms: pain, spasm, interference with daily activities, limitation of motion, and anxiety and tension (if present). A four-step severity rating scale was used: 1=none, 2=mild, 3=moderate, 4=severe. An overall average severity score was also calculated for each patient by dividing the sum of the individual symptom severity scores by the number of symptoms at baseline.

2. Objective evaluation of the degree of limitation of motion by measurement of the distance (in centimeters) from fingertips to floor following maximal forward flexion (finger to floor test).

3. Patient estimation of the intensity of pain by placing a mark on a "pain intensity scale" representing a continuum between "no pain" (0 percent) and "unbearable pain" (100 percent).

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*By Wallace Pharmaceuticals, Cranbury, New Jersey.

TABLE 4.—*Average Symptom Scores and Significance of Differences at Baseline*

		Average Scores			*Baseline Differences*	
Parameter	*Days on Drug*	*Carisoprodol (N=14)*	*Placebo (N=14)*	*Butabarbital (N=15)*	*Prob: Carisoprodol vs. Placebo*	*Butabarb.*
Pain	Base	3.5	2.9	3.1	0.02	0.09
	2	2.4	3.0	2.9		
	4	2.1	2.9	2.6		
Spasm	Base	3.1	3.0	3.1	>0.25	>0.25
	2	2.4	2.9	2.8		
	4	1.8	2.9	2.6		
Interference with Daily Activities	Base	3.7	3.1	3.3	0.02	0.07
	2	2.4	3.1	2.9		
	4	1.8	3.4	2.7		
Limitation of Motion	Base	3.3	2.9	3.1	0.12	>0.25
	2	2.0	3.1	2.9		
	4	1.6	2.9	2.7		
Anxiety and Tension	Base	2.6	2.2[1]	2.4[2]	0.16	>0.25
	2	1.9	2.2[1]	2.2[2]		
	4	1.6	2.4[1]	2.2[2]		
Global Average Severity	Base	3.3	2.9	3.0	<0.01	0.04
	2	2.2	2.9	2.8		
	4	1.8	2.9	2.6		
Finger to Floor (cm)	Base	33.3	27.0	24.3	0.14	0.04
	2	17.6	27.6	22.0		
	4	13.7	25.7	18.9		
Patient Estimate of Pain Intensity (%)	Base	86.0	65.5	75.2	<0.01	0.01
	2	33.0	58.5	58.7		
	4	15.5	64.0	49.1		

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[1] N=11 (3 placebo patients without anxiety and tension)

[2] N=12 (3 butabarbital patients without anxiety and tension)

Key:

Probability ≤ 0.05: significant difference between drug groups.

Probability >0.05 and ≤ 0.10: borderline significant difference between drug groups.

Probability >0.10: no significant difference between drug groups.

4. Final evaluation by the investigator of overall patient improvement. Global results were rated as:

Excellent=75 percent to complete relief of all symptoms with return to full activity.

Good=50-75 percent improvement in all symptoms with return to full activity.

Fair=25-50 percent improvement in all symptoms with some discomfort in doing daily activities.

Poor=Some improvement, but less than that described above.

Worse=Symptoms more severe than before entry into study.

Statistical Analysis

The Mann-Whitney U-Test was used to analyze the data of the carisoprodol as compared with the butabarbital group, and the carisoprodol against the placebo group, for each factor and for the overall evaluation.

Results

Symptomatic improvement: Table 4 shows the actual average symptom scores for each of the three test groups at baseline and at two and four days after the start of medication. Initial symptom severity scores are shown to have been higher for several factors in the carisoprodol group than in either of the other groups.

Table 5 shows the calculated improvement scores, and the statistical significance of differences between carisoprodol and placebo, and between carisoprodol and butabarbital. The analysis shows that:

1. Carisoprodol produced significantly greater relief of all symptoms—pain, spasm, interference with daily activities, limitation of motion, anxiety and tension $(P \leq 0.02)$—as well as greater overall average relief of these symptoms $(P<0.01)$ than placebo. Carisoprodol produced significantly greater objective improvement in the finger to floor test $(P=0.01)$, and greater reduction in

TABLE 5.—*Improvement of Measured Factors*

		Average Improvement			*Probability*	
Parameter	*Days on Drug*	*Carisoprodol (N=14)*	*Placebo (N=14)*	*Butabarbital (N=15)*	*Carisoprodol vs. Placebo*	*Carisoprodol vs. Butabarbital*
Pain	2	1.1	−0.1	0.2	<0.01	<0.01
	4	1.4	0.0	0.5	<0.01	0.01
Spasm	2	1.0	0.1	0.3	0.02	0.10
	4	1.3	0.1	0.5	0.01	0.02
Interference with Daily Activities	2	1.3	0.0	0.4	<0.01	0.01
	4	1.9	−0.3	0.6	<0.01	<0.01
Limitation of Motion	2	1.3	−0.2	0.2	<0.01	<0.01
	4	1.7	0.0	0.4	<0.01	<0.01
Anxiety and Tension	2	0.7	0.0[1]	0.2[2]	0.01	0.03
	4	1.0	−0.2[1]	0.2[2]	<0.01	0.04
Global Average Severity	2	1.1	0.0	0.2	<0.01	<0.01
	4	1.5	0.0	0.4	<0.01	<0.01
Finger to Floor (cm)	2	15.7	−0.6	2.3	<0.01	<0.01
	4	19.6	−1.3	5.4	0.01	0.02
Patient Estimate of Pain Intensity (%)	2	53.0	7.0	16.5	<0.01	<0.01
	4	70.5	1.5	26.1	<0.01	<0.01

[1] N=11 (3 placebo patients without anxiety and tension)

[2] N=12 (3 butabarbital patients without anxiety and tension)

Key:

Probability ≤0.05: significant difference between drugs
Probability >0.05 and ≤0.10: borderline significant difference between drugs
Probability >0.10: no significant difference between drugs

the intensity of pain experienced by the patient ($P<0.01$).

2. Carisoprodol also proved significantly more effective than butabarbital in improving all the factors measured ($P\leq 0.04$), except that the difference for relief of spasm was borderline ($P=0.10$) at the end of day 2.

Overall Improvement. Final evaluation of overall response to therapy in each of the three groups (Table 6) showed carisoprodol to be statistically significantly more effective than both placebo and butabarbital ($P<0.01$):

Side Effects. One patient receiving butabarbital had drowsiness and dropped out of the study after taking six tablets. No other adverse experiences were noted for any of the patients in this study.

Discussion

An unexpected finding, upon analysis of the data, was that, despite careful randomization, the baseline symptom severity scores for the carisoprodol group were significantly higher for several factors than were the baseline scores of either of the other two treatment groups. Apparently the sample size was simply not large enough to produce comparability of all factors in each of the groups.

The question of what influence this disparity may have had on the outcome is provocative, but probably not completely answerable. On the one hand, the scoring system favored a possibility for greater improvement in the group with greater initial symptom severity, since improvement was calculated by subtracting scores at each evaluation period from baseline scores. On the other hand, it is common clinical experience that severe pain is harder to relieve, and requires more potent medication, than mild pain. Thus the better performance of carisoprodol in this more severely ill group would tend to strengthen the meaning of the results. My own judgment is that, even though the method of scoring and analysis favored the more severely ill carisoprodol group, the magnitude of the difference in results between it and the other two groups was such as to represent a genuine superiority of this treatment over the others. This conclusion is supported by the fact that the critical symptom

TABLE 6.—*Comparison of Ratings, all Factors Combined*

Overall Response	*Carisoprodol*	*Butabarbital*	*Placebo*
Excellent	7	0	0
Good	5	2	2
Fair	0	6	1
Poor	1	6	5
Worse	1	1	6
Total No. of Patients	14	15	14

Carisoprodol significantly better than butabarbital (P <0.01)
Carisoprodol significantly better than placebo (P <0.01)

"spasm" showed significantly greater improvement with carisoprodol than with either butabarbital or placebo, despite the fact that the initial severity scores for this symptom were closely comparable in the three groups.

Conclusions

Since carisoprodol was shown to be significantly more effective than placebo in relieving the symptoms of the "low back syndrome," it can be concluded that it is an active medication, useful for the relief of pain and spasm in acute traumatic musculoskeletal conditions such as those treated. Since carisoprodol was found to be significantly better in all factors measured than butabarbital in the dosage used, it can be concluded that its effectiveness is not due solely to a sedative action, but is also related to its muscle relaxant activity.

TRADE AND GENERAL NAMES OF DRUGS

Soma®	carisoprodol

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THE PUS AND THE HISTORY?—TREAT FOR GONORRHEA

I am one of those individuals who feel that the diagnosis of gonorrhea is essentially clinical. Laboratory work helps but I still like to go back to the patient and get a history. I still like to look at the patient and see if he has the disease rather than rely solely on laboratory tests. The male who has a thick, creamy, yellow, purulent discharge, pain on urination, and a history of recent sexual exposure has gonorrhea; and somebody will have to prove to me that he doesn't. The female who has an endocervicitis and a little abdominal pain when you flip her uterus around, particularly if she has a history of promiscuous sexual exposure, also has gonorrhea. Both the female and the male are treated in our clinics on clinical evidence. We obtain smears and cultures and send them to the laboratory. But we make up our minds when we see the patient as to whether we are dealing with possible gonorrhea. We make a clinical diagnosis and institute therapy on the first visit, if at all possible. I believe we have to bend over backward and probably "overdiagnose" and then institute therapy immediately, particularly in the present epidemic situation.

—WALTER H. SMARTT, M.D., Chief, Venereal Disease Control Division, Los Angeles County Health Department, Los Angeles Extracted from *Audio-Digest General Practice,* Vol. 19, No. 24, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles 90057

Refer to: Calcaterra TC, Zwitman DH: Vocal rehabilitation after partial or total laryngectomy. Calif Med 117:12-15, Aug 1972

Vocal Rehabilitation after Partial or Total Laryngectomy

THOMAS C. CALCATERRA, M.D.,
AND DANIEL H. ZWITMAN, PH.D., *Los Angeles*

■ *One of the paramount concerns of a patient who must undergo surgical intervention for laryngeal cancer is the effect on his speech. The type of operation is based on the anatomic extent of the cancer, but each procedure presents inherent problems in vocal rehabilitation. Glottic incompetence is the primary deficit to be overcome following hemilaryngectomy, whereas the aspirate voice is the principal problem with supraglottic laryngectomy. When the larynx must be sacrificed by total laryngectomy, the patient attempts to learn esophageal speech. If this fails, a vibrating sound source for speech can be acquired, either by the construction of a trachealpharyngeal communication or by use of a manual electric vibrator.*

WHEN A PATIENT MUST BE TOLD that he has a laryngeal cancer, the devastating impact can be softened by reassurance that he has a good prognosis for life and an excellent outlook for speech after treatment. More than half of these patients can be treated by irradiation or by a surgical procedure that will spare one or both vocal cords. The others will require total laryngectomy but even then methods of speech without a larynx usually may be acquired with proper training.

Small, superficial vocal cord cancers commonly are treated by irradiation, usually without significant change of the quality of the voice. The patient may experience vocal fatigue, slight involuntary changes in vocal pitch, and impairment of precision vocalization such as singing. The patient should be counseled in proper vocalization and cautioned against vocal abuse.

More extensive cancers confined to the vocal cords are best treated by hemilaryngectomy. Since most vocal cord cancers are well differentiated and not deeply infiltrating, the surgeon can often spare the arytenoid cartilage of the involved vocal cord, improving the patient's chances for good vocal rehabilitation. Glottic closures may be accomplished by the remaining vocal cord, provided there is sufficient tissue filling the defect of the excised vocal cord. Various methods for providing adequate tissue (pseudocord) in the area of the excision have utilized muscle[1] and cartilage implants,[2] pyriform sinus mucosal flaps,[3] and cervical skin flaps.[4]

Success in vocalization depends largely on how straight and to what extent the pseudocord approaches the midline. Normal phonation requires complete approximation of the edges of both vocal cords. Injection of polytef (Teflon®) paste has proved to be very effective in filling irregularities and displacing the pseudocord to the midline.[5] Web formation or granulation tissue

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Submitted July 30, 1971.

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within the laryngeal lumen occasionally hampers vocal rehabilitation. Granulation tissue can be removed by simple excision, but the webbing may require use of a temporary intralaryngeal keel.

It is well known that the remaining vocal cord is capable of crossing the midline by one to two millimeters during phonation. This overcompensation can be augmented by certain vocal exercises which stimulate vocal cord abduction. Controlled coughing, strong phonation of select syllables such as "kik," and staccato vocalization of vowels all produce this effect. Pushing exercises described by Froeschels and associates[6] are based on reflex vocal cord abduction that occurs with certain motions of the arms and shoulder girdle. With strenuous arm pushing and pulling, glottic closure helps stabilize the thoracic cage. Similarly, vocal cord adduction can be elicited by instructing the patient to clasp his hands at chest level and then forcibly to push them downward while phonating "ah," or by having the patient push against an immovable object while phonating.

Limiting the Length of Phrases

Despite incomplete glottic closure with premature exhaustion of breath supply, most patients attempt word phrases of the length to which they were accustomed before they were operated upon. Consequently, each phrase ends in a forced whisper. The speech therapist stresses maximal inhalation, controlled exhalation, and shortened word phrases to help provide a more normal speech. The patient's pitch range is sampled to determine whether a particular pitch is less hoarse and strained. Early in therapy, maneuvers such as turning the head or pressing manually on the side of the neck improve phonation.

Cancers that arise above the vocal cords in the larynx and pharynx often can be extirpated by a supraglottic laryngectomy which spares the vocal cords (Figure 1). The patient who has an operation of this type may anticipate a nearly normal voice. There may be a loss of vocal pitch range, particularly in the upper registers, because of the necessary section of the nerve to the cricothyroid muscle which tenses the vocal cords. Occasionally the voice will have an aspirate quality due to oropharyngeal secretions on the vocal cords resulting from the loss of the supraglottic sphincteric action of the epiglottis and aryepiglottic folds. The patient usually can clear these secretions by exhaling slightly before speaking. A surgical method of tilting the larynx posteriorly 45 degrees by suture suspension to the mandible recently has been devised which augments spill-off of secretions on the vocal cords.[7]

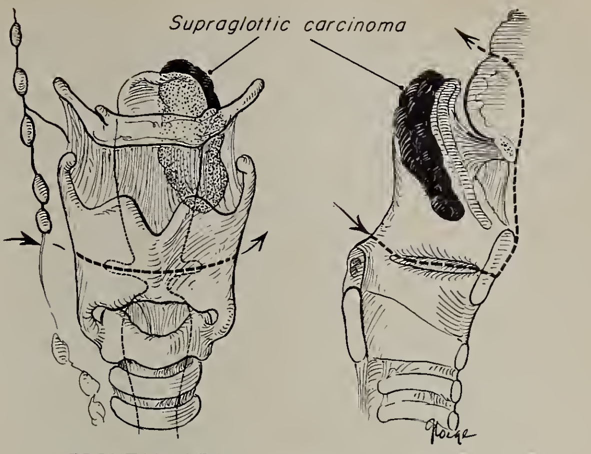

Figure 1.—Schematic views of the area of excision by supraglottic laryngectomy.

After Total Laryngectomy

Extensive cancers of the larynx that cannot be cleared by partial laryngectomy require total laryngectomy. Any method of vocal rehabilitation after total sacrifice of the larynx must produce a vibrating air column which can be formed into words by the articulating organs of the oral cavity. The most popular method of vocal rehabilitation is esophageal speech which utilizes the sphincter of the esophageal inlet as a vibrating sound source. The patient is trained to force air into the upper esophagus in a swallowing action and to release this air in a controlled manner through the cricopharyngeal sphincter which acts as a vibrating "pseudoglottis." The resultant speech is remarkably similar to normal laryngeal speech.

Low fundamental pitch and weak intensity are two major limitations of esophageal speech that undermine speech intelligibility. To alleviate these problems, the speech therapist trains the patient to phonate at average pitch levels (above 60 cycles per second) and, in addition, to fluctuate vocal pitch and intensity in order to relieve the monotony inherent in esophageal speech. Some esophageal speakers achieve a

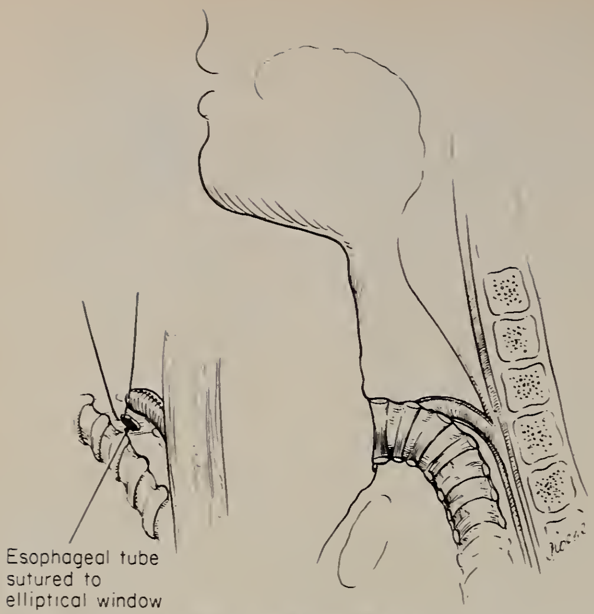

Figure 2.—The esophageal tube is sutured to a window excised in the trachea. A vibrating air column enters oral cavity through the esophageal tube.

vocal range of one octave. Since a limited volume of air can be expelled by the esophagus, the number of words between air intakes is a good deal less than with normal speech. The esophageal speaker is trained to limit words per phrase to five, rather than to end longer phrases in a forced whisper. This limited air supply also compromises sibilant consonants such as "s" and "sh," and there is complete loss of the "h" sound at the beginning of a syllable. Facial grimacing and the noise of esophageal air intake are other problems which the patient frequently can be trained to overcome.

If Esophageal Speech Fails

Despite adequate speech rehabilitational training, only 50 percent of persons who have had laryngectomy learn intelligible esophageal speech.[3] The training usually requires three to six months. The most common cause of failure to acquire speech of this type is an inability to achieve adequate relaxation of the esophageal sphincter, which can be restricted by scarring, severed nerve supply, or extensive surgical resection. Pharyngolaryngectomy or heavy irradiation to the cervical esophagus usually precludes acquisition of esophageal speech. Impaired hearing will interfere with the monitoring of speech, and frailty or old age make esophageal speech extremely difficult. Certain sequelae of esophageal speech related to air ingestion that may hamper its successful use include abdominal distension, excessive flatulence, and even gastric or duodenal ulceration.

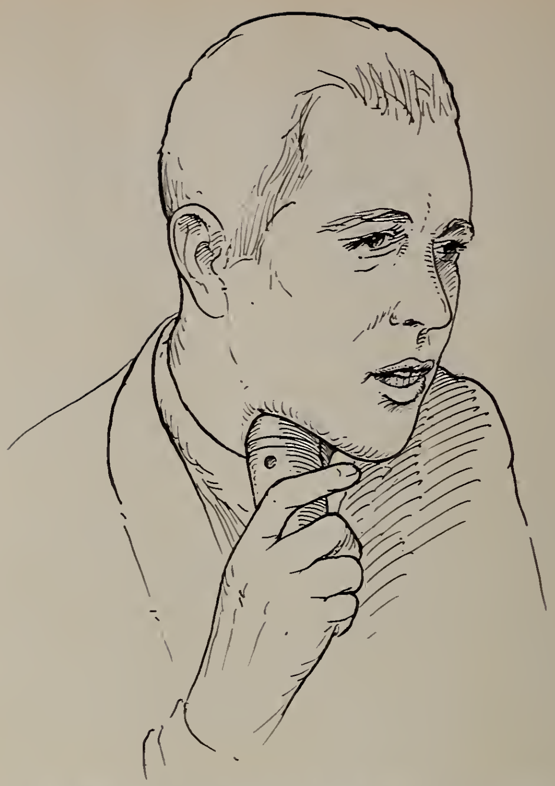

Figure 3.—The vibrating head of the electrolarynx is placed against the neck. The resultant tone is articulated into words by the oral cavity.

For patients who are not likely to learn esophageal speech, surgical procedures have been devised to generate a vibrating column of air sufficient for speech. It is known that if a communication can be developed between the trachea and pharynx, the vibration of air through this passage can be used for word production. Mechanical devices with a vibrating reed were used for a time but were discarded because of poor tissue tolerance.

Conley[9] used an autogenous vein graft, and Asai[10] constructed a cervical skin tube to create an air communication between the trachea and pharynx. By plugging the tracheostoma temporarily, the patient, on exhalation, is able to phonate with nearly normal quality. With both procedures, early success has been achieved in voice production; however, stenosis and aspiration through the communication have limited their use in many patients. One of the authors[11] has tested a full-thickness esophageal tube both clinically and in the laboratory that appears to solve the long-term problem of aspiration and stenosis (Figure 2).

The Electrolarynx

The sound source also may be generated by a battery-powered vibrating instrument called an artificial larynx or electrolarynx. The individual speaks by placing the vibrating head of the instrument against the side of his neck and articulating words with the tongue and oral cavity (Figure 3). Although the intelligibility is acceptable, many patients refuse this type of rehabilitation because of the unnatural mechanical quality of the resultant speech.

Early use of an electrolarynx remains a controversial subject. Some speech therapists feel that early reliance upon the electrolarynx will decrease motivation in the often arduous acquisition of esophageal speech. Contrasted against this consideration is the psychological impact of protracted silence and the economic necessity of resuming employment. We feel that the instrument need not interfere with esophageal speech, provided the patient undertakes early and regular speech therapy.

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ON BLEEDING AND REPLACEMENT AND BALDERDASH

The old axiom that if you bleed whole blood you should return whole blood is pure balderdash. Blood contains a variety of cells and a huge variety of proteins. If you make the assumption that when you bleed whole blood you are bleeding elements of equal life span, equal turnover rate, equal excess over physiologic need, equal degree of reserve, and equal "handleability" in the bottle or bag, then you would be quite right in stating that if you bleed whole blood you should return whole blood.

But actually whole blood contains red cells that live for four months, white cells that live for four hours, platelets which live for a week but are in enormous reserve (as are the granulocytes while red cells are in no reserve) . . ., and plasma proteins that have life spans of anywhere from a couple of days to a couple of months. What is more, these elements, when removed and placed in a storage container, may have a lifespan of hours. As a matter of fact if you take leukocytes from fresh whole blood, most are dead within a matter of several hours. Of those still alive at the time of retransfusion, 90 percent do not survive. On the other hand, if red cells are taken fresh from an individual and returned the same day, virtually 100 percent survive. Platelets are somewhere in the middle; about 50 percent survive. That being the case if one has a massive bleed and attempts to correct it with whole blood, at least half the platelets are lost in storage and a little bit more if the blood is more than four or five hours old.

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Death from Obstetrical Hemorrhage

HOWARD HAMMOND, M.D., *San Rafael*

■ *Twelve hundred nineteen maternal deaths occurring from 1957 through 1966 in the State of California have been reviewed by the Maternal Mortality Committee of the California Medical Association and the Bureau of Maternal and Child Welfare of the State of California. In 56 of these deaths the underlying causes were due to disorders of placental separation and placental bed hemostasis. Each of these 56 cases has been analyzed. Profiles of characteristics of patients dying from placenta previa, placenta abruptio, and uterine atony are given. The expected causes of death due to delay in giving adequate amounts of blood and fibrinogen occurred in this series but the most striking results of this study were the findings of (1) a large number of cases of placenta acreta in patients with repeat cesarean sections and (2) the lack of manual exploration of the uterus in many patients dying from uterine atony.*

OBSTETRICAL HEMORRHAGE OF ALL TYPES continues to be a leading cause of maternal death, as noted in recent publications based on data from hospitals and public health departments. Reports from hospitals such as Magee-Womens,[1] Columbia-Presbyterian,[2] Cook County[3] and the Royal Alexandria[4] (Edmonton) include patients who survived the hemorrhages as well as those who died. Reports from health departments, such as those in Oklahoma,[5] British Columbia,[6] the District of Columbia,[7] and North Carolina,[8] are based on deaths alone and include patients who had no medical care or who died before reaching a hospital.

Page[9] has questioned the value of studies, such as the last four mentioned, where the "selection as the end point is only the patients who died." This might be a valid criticism if studies emanating from hospitals[1-4] had enough deaths to provide sufficient information to point out the avoidable factors causing deaths. The reports derived from health departments based on deaths do just that.

Cook County Hospital[3] was the only one of the four hospitals[1-4] to report any deaths since World War II from disorders of the placental bed or uterine atony. All other hemorrhagic deaths were secondary to trauma or occurred before the twentieth week of gestation. However, the reports emanating from the public health departments[5-8] contained a number of deaths due to primary hemorrhage. The British Columbia[6] series showed 50 percent of postpartum hemorrhage deaths were in native Indians who made up only 2 percent of the total population. Patient responsibility was most often the primary avoidable factor in this group.

Fraser,[7] from the District of Columbia, reported 3.5 percent of maternal deaths were due to atony, placenta previa, or abruptio placentae.

This report concerns deaths due to obstetrical hemorrhage investigated by consultants of the

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Presented at the 37th Annual Meeting of the Pacific Coast Obstetrical and Gynecological Society, Kauai, Hawaii, November 9 to 14, 1970.

Submitted November 16, 1971.

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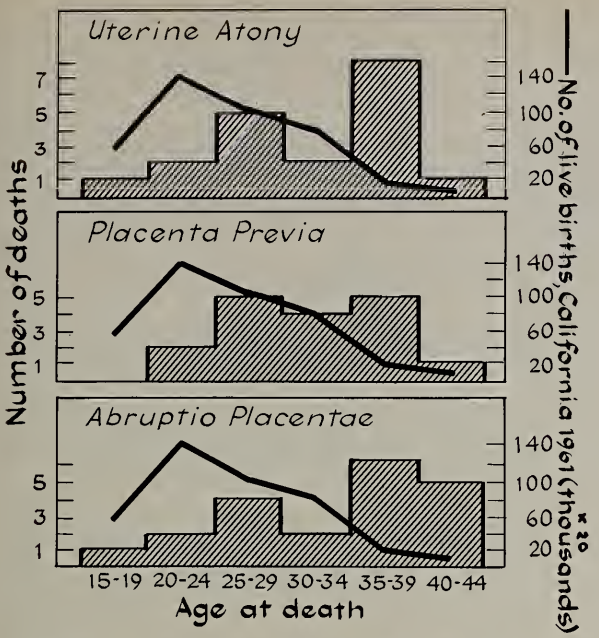

Chart 1.—Distribution by age at death from obstetrical hemorrhage related to uterine atony, placenta previa and abruptio placentae, compared with age distribution of all live births in California during 1961.

Bureau of Maternal and Child Health of the California Department of Public Health. The protocols were reviewed by the Maternal Mortality Committee of the California Medical Association, as previously described by Montgomery.[10] The characteristics and the management of women who were victims of the three major causes of obstetrical hemorrhage, namely, uterine atony, placenta previa and abruptio placentae, are analyzed in this report.

From August 1957 to December 1966 the California Maternal Mortality Committee reviewed 1,219 deaths, or approximately 90 percent of all maternal deaths that occurred during the study period. Of this number, 85 were due to obstetrical hemorrhage (International Causes of Death 643-4 and 670-2). This does not mean that only 85 women bled severely, for at least 455 of the patients studied had transfusions. It means that in 85 instances the underlying cause of death was uterine hemorrhage *per se,* not bleeding provoked by trauma. Hemorrhages due to trauma of the birth canal, uterine rupture (77 cases during the study period) and other causes of maternal death not included in those code numbers are not considered. The records of 56 women who died because of hemorrhage due to postpartum uterine atony (19 cases), abruptio placentae (20 cases) and placenta previa (17 cases) have been reviewed in detail. This makes up 4.6 percent of related maternal deaths during the study period. During this time there were more than three million live births in California.

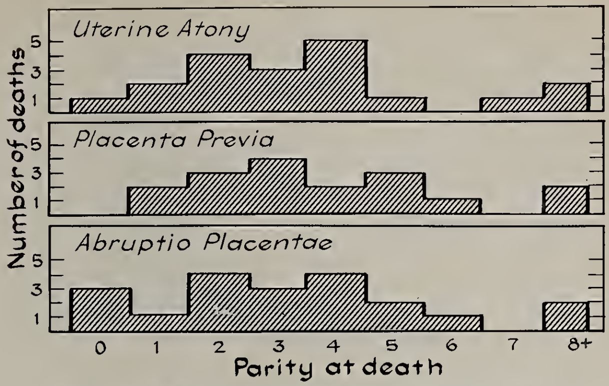

Chart 2.—Parity at death from hemorrhage due to uterine atony, placenta previa and abruptio placentae.

Chart 1 shows the age distribution of patients with the various causes of hemorrhage. The superimposed line graph shows the number of deliveries for each age category in 1961 (the middle year of the study). This graph emphasizes the increased numbers of deaths in the older women, especially after age 35.

Chart 2 shows the parity at death, not including the present pregnancy. It is to be noted that there are no deaths from placenta previa among primigravidas, but in this group there were three cases of abruptio. Most of the patients were in their third, fourth and fifth pregnancies. A graph of parity for all deliveries would show the greatest number with first pregnancies and diminishing abruptly after two deliveries.

Chart 3 shows that fatal hemorrhage occurs predominantly after the thirty-ninth week in both atony and abruptio. However, with placenta previa all but one case of fatal hemorrhage occurred earlier in gestation.

Table 1 details the method of delivery. Two-thirds of the women with atony delivered spontaneously, but 15 of the 17 previa cases were delivered by cesarean section. Those with abruptio were equally divided among the undelivered, vaginally delivered and cesarean section categories.

Table 2 shows the units of blood given. Seventeen patients received either no blood or only a single unit. Fifteen patients in each group received one or more units of blood.

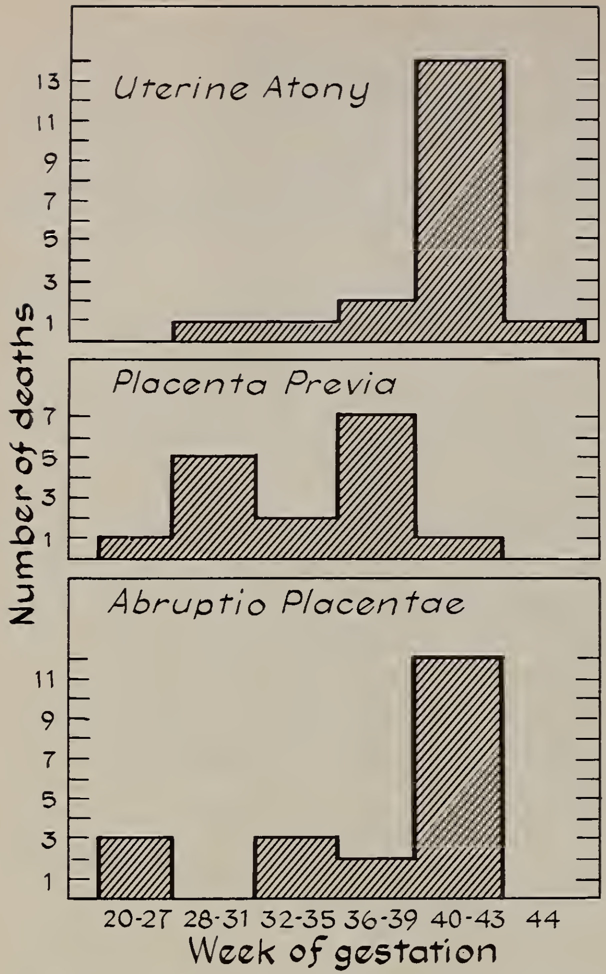

Chart 3.—Distribution of deaths from uterine atony, placenta previa and abruptio placentae, by weeks of gestation.

TABLE 1. ***Methods used to deliver 56 women who died from hemorrhage related to uterine atony, abruptio placentae and placenta previa***

Method	*Number of Patients*		
	Atony	*Previa*	*Abruptio*
Undelivered	0	0	6
Spontaneous	13	2	6
Forceps	5	0	1
Breech	1	0	0
Primary cesarean section	0	6	6
Repeat cesarean section	0	9	1
Total	19	17	20

TABLE 2. ***Units of blood used to transfuse women who died of obstetrical hemorrhage***

Number of 500 ml units given	*Number of Patients*		
	Atony	*Previa*	*Abruptio*
0	4	2	5
1	4	0	2
2 to 10	9	10	13
Over 10	2	5	0
Total patients	19	17	20

Chart 4 shows that a majority of the patients with atony died within four hours, possibly before the seriousness of the hemorrhage was fully realized. Fatal hemorrhage occurred after a longer time in many of the abruptio cases but the amount of blood given was about the same as in the atony group. In the previa cases, the largest number of deaths took place 8 to 16 hours after onset of bleeding, thus there was more time for transfusions.

Table 3 details the surgical treatment. All patients who had any medical care were given some form of oxytocin. In nine of the atony cases, the uterus was not explored and two of the patients had no medical care at all. Ten of the abruptio patients had no surgical treatment. In the previa series, there were 15 cesarean sections or cesarean-hysterectomies. The reviewing committees noted that in four cases in which incisions were made through the placenta, rapid exsanguination followed. In belated attempts to save lives, hysterectomy was performed in 11 cases after the patients were virtually moribund. In addition, there were two exploratory laparotomies, one eight hours after a cesarean-hysterectomy and one immediately after spontaneous delivery of a patient with placenta previa.

The fate of the fetus is shown in Table 4. In the atony group, 16 of 19 infants survived, but only four out of 20 in the abruptio group—where six women died undelivered. Cesarean section was done post mortem in the case of one of the women who died undelivered. The baby died almost immediately but this must be listed as a neonatal death.

Table 5 shows the other causes contributing to death. By far the most common was afibrinogenemia. Only six patients received more than 7 grams of fibrinogen. All of the cases of amniotic fluid embolism were proved at autopsy and in two others this diagnosis was suspected but no autopsy was done. The autopsy rate for the entire series was 55 percent.

Two cases of uterine rupture are listed but this was not the primary cause of death in either instance. One placenta previa had incidentally eroded through the uterus. In one abruptio case, the rupture was also secondary.

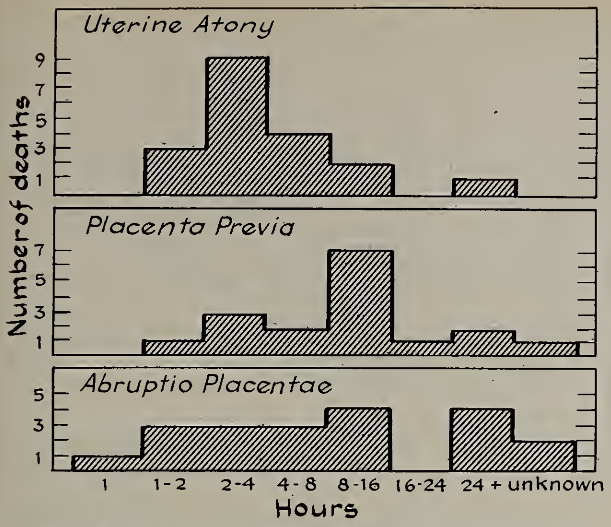

Chart 4. Distribution of deaths from uterine atony, placenta previa and abruptio placentae, by hours from onset of final bleeding episode to time of death.

TABLE 3. ***Surgical procedures used in 56 women who died of obstetrical hemorrhage***

Procedure	*Number of times used in patients with*		
	Atony	*Previa*	*Abruptio*
None	9	1	10
Manual exploration of uterus	10	0	2
Cesarean section	0	11	6
Cesarean-hysterectomy	0	4	1
Hysterectomy in extremis	4	7	0
Exploratory laparotomy	0	2	0
Thoractomy	0	3	3

TABLE 4. ***Fate of fetus in women who died of obstetrical hemorrhage***

Fetal Fate	*Number of Patients*		
	Atony	*Previa*	*Abruptio*
Undelivered	0	0	5
Stillborn	3	5	9
Neonatal death	0	4	2
Survived	16	8	4
Total	19	17	20

TABLE 5. ***Contributing causes of death of 56 women who died of obstetrical hemorrhage***

Contributing Disorder	*Number of instances with*		
	Atony	*Previa*	*Abruptio*
Afibrinogenemia	5	6	7
Placenta accreta	0	6	0
Amniotic fluid embolus	0	1	4
Pre-eclampsia	0	2	1
Cardiac arrest	2	1	0
Uterine rupture	0	1	1
Hidden hemorrhage	0	1	1
Septicemia	1	1	0
Other medical disorders	4	1	3

Placenta accreta was present in six of the 17 women with placenta previa. All patients were having at least the third baby. Two were having their first cesarean section and others their third, fourth or fifth. Only one case of abruptio was associated with pre-eclampsia, and this was very mild—a rather unexpected finding. Also unusual is the fact that only two patients had septicemia.

Table 6 lists the avoidable factors. While physician errors were mostly of the "too little and too late" variety, the patient factors were mostly failure to seek care or outright refusal to accept care. Physician errors were most apparent in ordering too little blood or fibrinogen, or giving these products too late. Exploration of the uterus was not done in nine atony cases. Surgical treatment in previa cases was either too late or errors were made in technique. This can be expected when operation was performed not only in teaching hospitals but also in small hospitals in rural areas. Most of the cases were classified as unavoidable deaths when amniotic fluid embolism followed the onset of hemorrhage.

The following descriptions are profiles of the patients in this series who died from one of the major causes of obstetric hemorrhage:

Atony (19 cases): An elderly multipara at term delivered spontaneously, and bled to death usually within four hours, after inadequate blood replacement. Surgical treatment, including exploration of the uterus, was not done in 45 percent of the cases. Twenty-five percent of the patients developed afibrinogenemia but received little or no fibrinogen. The fetus almost always survived. Avoidable factors were attributable to the patient in five cases and to the physician or facility in 15.

Abruptio placentae (20 cases): An elderly and usually multiparous patient, at term, equally likely to deliver spontaneously, remain undelivered, or be delivered by first cesarean section. The time of death after start of final hemorrhage ranged from one to sixteen hours, but during these hours 25 percent of patients received no blood at all. Thirty-five percent had afibrinogenemia and 20 percent had amniotic fluid embolus proved by autopsy, and only 20 percent of the fetuses survived. Avoidable errors were attributed to patients in five cases, to physicians in 11.

Placenta Previa (17 cases): Not quite as el-

TABLE 6. *Numbers of errors attributed to patients, physicians and physical facilities*

Error	Number of occurrences in cases of		
	Atony	*Previa*	*Abruptio*
Patient's judgment	5	2	5
Inadequate facilities	1	0	3
Physician's judgment	14	15	11
Diagnostic	3	7	4
Use of blood	8	9	7
Use of fibrinogen	4	4	4
Surgical procedure	7	11	5

derly as women with the other disorders, but all were multiparous and only one at term. Fifteen of 17 were delivered by cesarean section. Sixty percent of cesarean sections were repeats and 40 were in women who had had three or more previous sections. Almost two-thirds of patients lived eight hours or more, so time was available to procure and give blood in large amounts. In spite of so many sections, there were seven hysterectomies performed on women in extremis and two exploratory laparotomies. Only one patient had no surgical treatment. Afibrinogenemia and placenta accreta were common complications. About half of the babies survived. Errors were attributed to patients in two cases, to the physician in 15.

Discussion

Taylor,[2] who reported no deaths from hemorrhage at Sloane Hospital, lists four requisites for the treatment of uterine bleeding in pregnant women: (1) Observation in hospital if possible; (2) blood typed and available; (3) blood replaced early; and (4) fibrinogen given early and in adequate amounts.

Though emphasis on these requirements is important, it is not only necessary to replace blood and fibrinogen but to *stop the bleeding* by either medical or surgical means before serious loss of blood takes place. The North Carolina[8] report laid particular emphasis on this. As Mengert[11] said, the physician must have the moral courage to move to drastic action if necessary. In placenta previa, Semmens[12] believes delivery should be effected as soon as maternal circulation can be stabilized, regardless of gestational age, if bleeding exceeds 600 ml in any single episode. He advocates a low cervical incision with separation of the placenta rather than incision through it. In four cases of the series here reported, incisions were made through the placenta. Brock[13] believes placenta previa accreta is due to high parity and previous mechanical injury of the uterus. In the six cases here presented, two patients had had no previous surgical treatment but four had had previous cesarean sections and in two the uteri had been curetted. Parity in these women ranged from three to nine.

Essig[14] and his group at Ohio State, among others, advocate routine exploration of the uterus after the third stage of labor. Failure to explore the uterus after vaginal delivery was noted frequently in our series.

The present study confirms the futility of hysterectomy after the patient is in extremis. We have all seen cases of impending shock in ectopic pregnancy and then prompt rise in the blood pressure as soon as a hemostat is placed on the bleeding vessel. The same prompt improvement occurs in patients with uterine bleeding if judicious surgical treatment is provided at the appropriate time.

But the commonest preventable factor in death from obstetrical hemorrhage is neglect of the patient either by herself or by her physician. As long as the patient does not make herself available for care or the physician fails to be present, or fails to do all he can to care for the patient, we will continue to have deaths from obstetrical hemorrhage.

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Refer to: Fajardo LF, Sarasti H: Technique for percutaneous needle biopsy of bone and marrow. Calif Med 117:21-24, Aug 1972

Technique for Percutaneous Needle Biopsy of Bone and Marrow

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THE INDICATIONS FOR BONE MARROW aspiration are well known, and the need for bone marrow specimens obtained by excision instead of—or in addition to—aspiration is also well recognized. Rather than using the conventional open bone and marrow excision of biopsy specimens, more and more institutions are relying on obtaining the specimens percutaneously, which does not require operating room facilities.[1-4] Percutaneous bone and marrow sampling is currently used in the staging of lymphomas in Stanford Medical Center. It will be used more often as patients with other tumors, metabolic bone disease, and the like are more extensively evaluated.[5]

There are several instruments designed or adapted for this type of procedure.[6-12] One that has been gaining in popularity is the modified, large, Vim-Silverman needle (Westerman-Jensen model).[1,2,3] This is a satisfactory instrument, but many physicians are not familiar with it. Unfortunately we have not found a description of the technique that illustrates, with sufficient detail, the proper handling of needle and specimen.

The following method, which includes our modifications, has been used for several hundred biopsies carried out at San Juan de Dios, and Central Military Hospitals in Bogotá, Colombia, and at the Stanford University Hospital and its affiliated Veterans Administration Hospital of Palo Alto, California. This procedure has not resulted in any serious complications in more than 200 patients observed between one week and one year after biopsy. Emphasis will be made on those steps of the method where errors have been noticed most often.

Technique

The needle* used consists of the following parts: (Figure 1)

A. Needle shaft with beveled tip. Luer lock fits into B.
B. Needle obturator.
C. Cutting blades, with inner bevel. This is the most delicate part of the instrument.
D. Blades' stylet (used for ejection of specimen).

This biopsy method can be carried out at the patient's bed or in a physician's office. A half hour before the procedure, adult patients are given 50 mg of meperidine hydrochloride (Demerol®) intramuscularly. To assure his cooperation and to decrease his anxiety the patient must be told that the procedure is innocuous, although it may cause slight discomfort.

Most biopsy specimens have been obtained from the posterior and superior iliac spine, and the best position for an adult is the lateral decubitus. Individual circumstances may demand the sampling of other areas with abundant cancellous bone, such as the anterior iliac spine, but we do not recommend the use of this needle in the sternum. The technique used in children has been described by Pearson, McFarland and Cone.[13]

Flexion of the corresponding limb helps to determine by palpation the position of the bone

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*Large needle for bone and marrow biopsy (W-J model), Division of Special Needles, Becton-Dickinson Co., Rutherford, N.J.

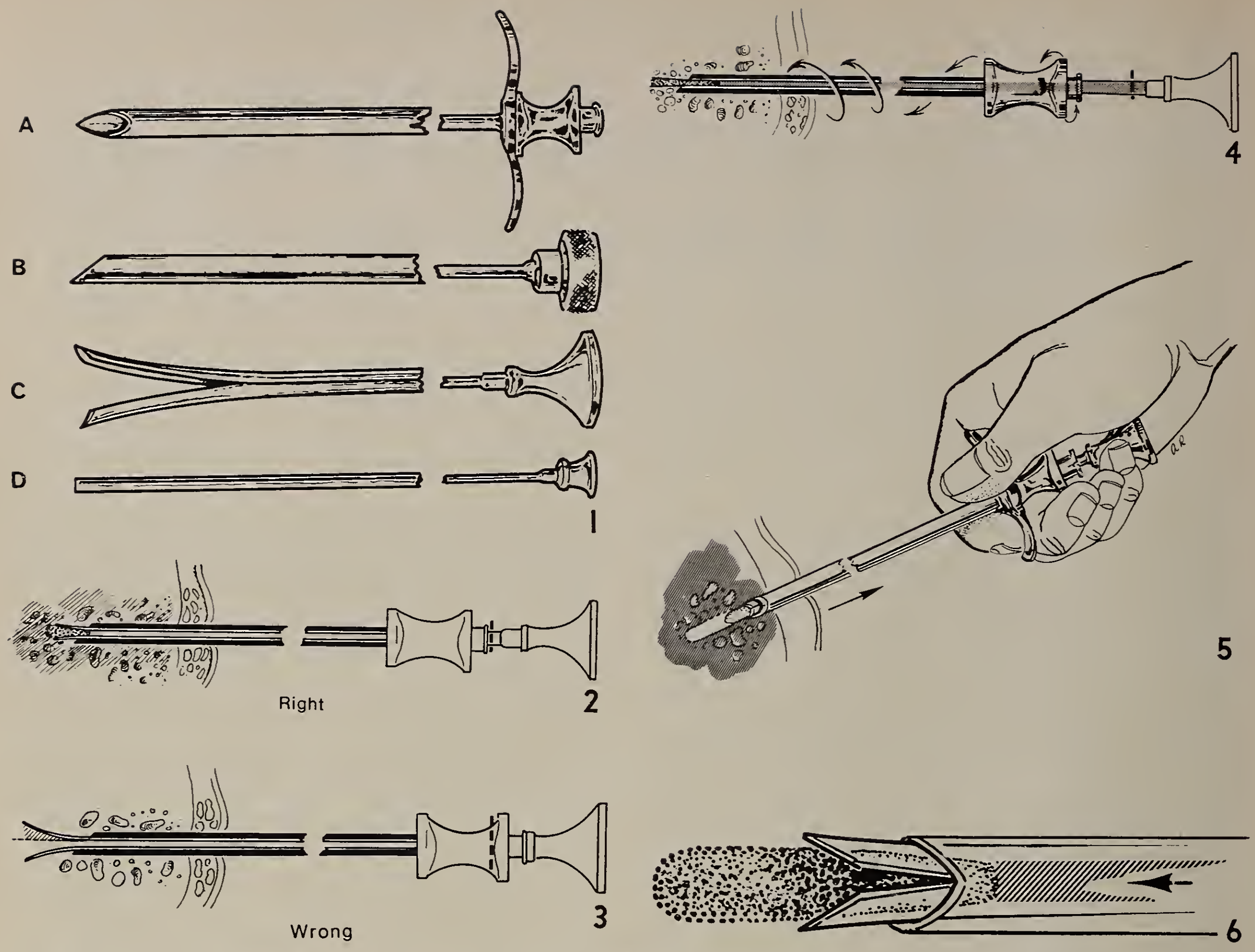

Figure 1.—Components of needle used in percutaneous excision of bone and marrow are shown in frame 1. The right and wrong depth of penetration of blades are shown in 2 and 3. Frame 4 illustrates the incomplete clockwise-counterclockwise rotation that is used in sliding the needle shaft down around the blades to grasp the specimen for withdrawal. Withdrawal (shown at 5) is carried out with the shaft kept close to the tip of the blades lest the specimen be damaged or lost. A slight clockwise-counterclockwise rotation facilitates extraction. The specimen is pushed out with the blades stylet (as shown at 6) onto a glass slide, where it is smeared before fixation.—Illustrations by Albert Rendes.

prominence. A small amount of 2 percent lidocaine hydrochloride (Xylocaine) without epinephrine is injected with a 22-gauge needle intradermally and at several points of the periosteum in, and immediately around, the area chosen for biopsy. A 5 mm longitudinal incision of skin is made with a No. 11 Bard-Parker blade.

The assembled needle (A and B) is inserted until it touches the bone. Then it is introduced into the bone with a clockwise-counterclockwise rotary motion. This step may require considerable pressure if the bone cortex is thick. To avoid lateral slipping of the needle and a useless biopsy of cortical tissue, it is necessary to keep the needle perpendicular to the bone surface. When it has penetrated through the cortex, the needle is firmly supported by the bone and does not need to be hand held. Only then can the next step be carried out.

The obturator (B in Figure 1) is unlocked, removed and replaced by the blades (C). This step is easier if the blades are inserted with their stylet (D), which is then removed.

Then the blades are introduced into the bone, *without rotation* and not more than 1 cm beyond the tip of the needle (see 2 in Figure 1). To assure that this length is not exceeded, a mark is etched on the surface of the blade (see broken line in illustrations 2, 3 and 4) where it can be kept in view and the depth of penetration gauged thereby. Penetration of the total length of the blades results in outward bending and damage of the instrument (see 3 in Figure 1); also the large bone "bite" cannot be removed. Gentle tapping with a mallet provides fast and accurate penetration.

Leaving the blades in place, the needle shaft is introduced around them by incomplete, clockwise-counterclockwise rotation (see 4 in Figure 1). The specimen is being cut free at this time and penetration of the needle shaft does not need to be more than 1 cm (that is, to the tip of the blades). Again, the blades *should not be rotated.*

The needle, now containing blades and specimen, is removed as a single piece—that is, avoiding displacement between shaft and blades, which could result in damage or loss of specimen (see 5 in Figure 1). This extraction is better accomplished by minimal clockwise-counterclockwise rotation.

The specimen is pushed out with the blades stylet (6 in Figure 1) onto a glass slide. Attempts to pull the sample with the blades *through* the needle will result in distortion of tissue. The sample generally is a cyclindroid of cancellous bone, up to 20 mm long, with a maximum diameter of 3 mm. Marrow is easily seen.

Satisfactory prints for cytologic examination are obtained by gently rolling the specimen on glass slides. Also good fragments of bone marrow can be scraped promptly from the inner surface of the blades and smeared. Thus, cytologic and histologic preparations can be secured from the specimen.

Serious histologic artefacts will occur in biopsy specimens obtained immediately after bone marrow aspiration of the same area. However, if aspiration is indicated it may be performed after the biopsy: a conventional bone marrow needle is inserted through the already anesthetized skin and periosteum, at a different angle in order to avoid the area of the biopsy.

After bacteriologic (if necessary) and cytologic preparations are completed, the specimen is immersed in Zenker's fixative[14] without acetic acid for two to four hours. Initially, we used fixation in 10 percent neutral formaldehyde, which was not as satisfactory. Bouin's fixative gives good results, but limits the range of staining procedures. After fixation, decalcification of this small specimen is accomplished generally in 30 minutes with 5 percent nitric acid solution (never more than one hour for normal cancellous bone). After a short period of washing in tap water the tissue is processed as usual for paraffin embedding. Longitudinal sections are stained in each case with hematoxylin and eosin, and for iron (Gomori's method).[14] Eosin stain is light, so differentiation between neutrophilic and eosinophilic granulocytes is easy. Many other stains, for collagen, reticulum, micro-organisms, etc., are performed according to the individual case.

As soon as the needle is removed, an assistant applies continuous pressure in the area with a gauze pack for five minutes. Afterward, a thick pack of gauze is left in place for 24 hours, supported by a wide strip of adhesive tape which must cover more than one-half of the pelvic girdle. Suture of the incision is not necessary.

This needle requires little maintenance, beyond careful cleaning immediately after each use. Sharpening of the cutting blades may be necessary from time to time. One of our first needles was used for more than 100 specimens before reconditioning was needed.

Indications

The following is a list of the indications for percutaneous needle biopsy of bone and marrow as compiled from our own experience[2] and a brief review of the literature.[3,4,5,7,9,11,15,16]

- Investigation of unsuccessful bone marrow aspiration ("dry tap").
- Diagnosis of myelofibrosis or osteosclerosis.
- Diagnosis of bone marrow hypoplasia or aplasia.
- Diagnosis or Staging of
  - Primary or metastatic tumors of bone marrow (leukemia, lymphoma, plasmacytoma, carcinoma, and the like).
  - Infectious diseases (tuberculosis, mycosis, etc.).
  - Reticuloendothelioses (histiocytosis X, Gaucher's disease, etc.)
- Study of metabolic bone disease.
- Follow-up of any of above conditions.

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Refer to: Geokas MC: Acute pancreatitis (Medical Progress). Calif Med 117:25-39, Aug 1972

Medical Progress

Acute Pancreatitis

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■ *For many decades two types of acute pancreatitis have been recognized: the edematous or interstitial and the hemorrhagic or necrotic. In most cases acute pancreatitis is associated with alcoholism or biliary tract disease. Elevated serum or urinary α-amylase is the most important finding in diagnosis. The presence of methemalbumin in serum and in peritoneal or pleural fluid supports the diagnosis of the hemorrhagic form of the disease in patients with a history and enzyme studies suggestive of pancreatitis.*

There is no characteristic clinical picture in acute pancreatitis, and its complications are legion. Pancreatic pseudocyst is probably the most common and pancreatic abscess is the most serious complication.

The pathogenetic principle is autodigestion, but the precise sequence of biochemical events is unclear, especially the mode of trypsinogen activation and the role of lysosomal hydrolases. A host of metabolic derangements have been identified in acute pancreatitis, involving lipid, glucose, calcium and magnesium metabolism and changes of the blood clotting mechanism, to name but a few.

Medical treatment includes intestinal decompression, analgesics, correction of hypovolemia and other supportive and protective measures. Surgical exploration is advisable in selected cases, when the diagnosis is in doubt, and is considered imperative in the presence of certain complications, especially pancreatic abscess.

"It is scant modesty for man, even if he is 'the highest vertebrate' to presume that he can predict the cosmic plan on the intensity of his joy and pain, or cement the stars together with even his highest aspirations."

Homer Smith. *From Fish to Philosopher;* Boston; Little, Brown, 1953.

The pancreatic acinar cell segregates the enzyme protein from the cytoplasm immediately after its synthesis in order to avoid autodigestion. The endoplasmic reticulum, the Golgi complex, the zymogen granule membrane and the cell membrane proper constitute an effective interposition device covering the entire secretory cycle of the acinar cell. The pancreatic proteases (trypsin, chymotrypsin, elastase and carboxypeptidases) and phospholipase A are stored in the acinar cell and exist in the pancreatic secretion,

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before it enters the duodenum, as inactive zymogen.[1,2] Trypsin plays the central role in the physiological activation of zymogen because the activation process consists of one or more trypsin catalyzed partial proteolysis reactions.[3] The stability of the entire zymogen system largely depends on the trypsin inhibitors which under normal conditions will prevent the trypsin activation of zymogen in pancreatic tissue and pancreatic secretion into the pancreatic ductal system.[4] Finally, healthy respiring acinar cells are not amenable to digestion by pancreatic proteases, because it has been shown that normal cell metabolism and cell membrane structure constitute important safeguards against enzyme-digestion.[5]

In acute pancreatitis inappropriate activation and release of enzymatic activity occurs in and around the pancreas[6,7] in pancreatic juice,[8] and into the blood stream.[9] The disease has been induced in various animals such as dogs, rats, cats, rabbits, goats and monkeys by a variety of methods, and certain forms of experimental pancreatitis bear some resemblance in microscopic pathologic features and in biochemical changes of the disease in man. Since the brilliant experiment of Claude Bernard in 1856,[10] two important questions remain unanswered, (1) how the various etiological factors initiate acute pancreatitis by overcoming the existing natural safeguards and (2) which mechanisms are responsible for the propagation of hydrolytic cleavage of cellular structures leading to generalized pancreatic necrosis and death.

Nonetheless, recent experimental and clinical data have provided some clues in the pathophysiology of acute pancreatitis and the time appears ripe to review previous information in the light of certain new developments. Since this review is mainly clinical, and recent reviews of etiological and pathogenetic mechanisms are available,[11,12] many important contributions will not be included. On the other hand, speculation and personal opinion on controversial points concerning pathophysiology, differential diagnosis, metabolic consequences and treatment will be discussed.

Etiology

Alcoholic Pancreatitis

The mechanism by which the heavy drinking of alcohol leads to acute attacks of pancreatitis remains unclear. Shapiro et al[13] have proposed a detailed hypothesis which includes stimulation of gastric acid secretion both by gastrin release in the antral mucosa and by direct stimulation of parietal cells. In turn, acid reaching the duodenum would promote secretion of secretin and pancreozymin with resultant stimulation of pancreatic secretion by all three gastrointestinal hormones. Concomitantly, a direct effect of ethanol on the sphincter of Oddi would increase sphincteric resistance[14-16] with resultant increase in intrapancreatic ductal pressure. Another proposed mechanism for alcoholic pancreatitis involves the reflux of bile into the pancreatic duct, but this suggestion remains at present purely hypothetical.[17] On the other hand, sphincteroplasty has been shown to reduce the incidence of pancreatitis even in patients who continue the intake of ethanol following this procedure,[18] a fact which probably indicates that reflux of bile does not play an important role in initiating alcoholic pancreatitis.

It has been shown that total obstruction of the pancreatic duct in dogs, combined with stimulation of pancreatic flow by endogenous or exogenous hormones, produces little pancreatic inflammatory response.[19] Recent studies suggest that a direct toxic effect of ethanol on the pancreas should be considered as at least partially involved in the production of pancreatitis. In the liver cells, structural changes have been described which probably represent a direct hepatotoxic effect of ethanol,[20-22] and it seems that a similarity exists between hepatic and pancreatic ultrastructural lesions, following the ingestion of ethanol in experimental animals. Darle et al[23] showed that in rats following long-term ethanol ingestion, the pancreas exhibited lipid droplets in acinar cells, swelling of mitochondria and reduction of their inner membranes, and cytoplasmic degradation of acinar and centroacinar and duct cells. Long-term ethanol ingestion is accompanied by decreased protein synthesis in the pancreas,[24] and by inhibition of uptake of ^{32}P into pancreatic phospholipids.[25] Furthermore, impairment of Na^+ dependent uptake of certain amino acids by pancreatic slices of alcohol-treated mice in vitro has been reported.[26] Further studies are required, however, to substantiate the direct toxic effect of ethanol on the pancreatic acinar cells and the mode of production of alcoholic pancreatitis.

Hyperlipidemia

Hyperlipidemia at times seen with acute pancreatitis may be (a) primary and a cause of pancreatitis, (b) secondary and a consequence of pancreatitis, and (c) a casual association with acute pancreatitis. Two of the primary hyperlipoproteinemias (type I and V) may be associated with bouts of abdominal pain due to pancreatitis.[27] Attacks of pancreatitis frequently begin in childhood and over the years lipemia retinalis, hepatosplenomegaly, and any of the many forms of xanthomas may be observed. Accurate classification of the lipid abnormality can usually be obtained with lipoprotein electrophoresis.[28]

Determination of lipoprotein lipase activity[29] is helpful in differentiating between type I and V. The cause of pancreatitis in familial hyperlipidemia is unknown. The episodes of acute pancreatitis are frequently mild and without severe complications.

Hypercalcemia

Hypercalcemia due to parathyroid adenoma,[30] parathyroid carcinoma[31] excessive doses of vitamin D,[32] multiple myeloma or calcium carbonate antacid overdose[33] might result in acute pancreatitis. The relationship between hypercalcemia and pancreatitis remains an uncertain one. Regardless of cause, hypercalcemia leads to an increase in calcium concentration and content in pancreatic juice. Data on experiments with dogs have shown that a rise in volume and bicarbonate concentration in pancreatic secretion is not accompanied by an increase in calcium concentration.[34,35] In patients with hyperparathyroidism there is increased calcium concentration in basal pancreatic secretion[36] and the same is true in experimental hypercalcemia in animals.[37] In chronic pancreatitis not related to hyperparathyroidism or hypercalcemia, there is high calcium content in basal pancreatic secretion.[36,38,39] It is noteworthy that the injection of soluble calcium compounds into the pancreatic ducts of rats results in severe acute pancreatitis.[40] In hyperparathyroidism acute pancreatitis has been attributed to conversion of trypsinogen into trypsin by high levels of calcium in pancreatic tissue and pancreatic secretion. Thus, in hypercalcemic rats increased levels of trypsin were found in pancreatic juice,[37] but no similar observation has been made in man. Pancreatic calcification is common in pancreatitis associated with alcoholism[41,42] hyperparathyroidism,[43,44] hereditary pancreatitis,[45,46] pancreatitis secondary to a duct obstructing pancreatic carcinoma,[43] rarely in pancreatitis accompanying biliary tract disease[41] and quite frequently in painless pancreatitis.

Solitary calculi obstructing the main pancreatic duct represent a variant of painless pancreatitis. The predominant form of calcium salt precipitation in the pancreas is calcium carbonate into the ducts, and less common is hydroxyapatite calcification deposited in areas of fat necrosis in the parenchyma.[47]

Biliary Tract Disease

The causative factors involved in the association of biliary tract disease and acute pancreatitis remain obscure. Recent work has focused on two areas of investigation: (a) the reflux into the pancreatic duct of altered components of bile such as unconjugated bile salts[48] and lysolecithin,[49] and (b) the identification of lymphatic channels as a pathway for the propagation of toxins with resultant pancreatic inflammation.[50] Deconjugation of conjugated bile salts could be effected by certain bacteria[48] and lysolecithin could be produced by the phospholipase A of pancreatic secretion acting upon bile lecithin.[49]

In one study unconjugated bile salts were detected in bile of patients with acute pancreatitis associated with gall bladder disease; and in another study,[51] of patients with acute cholecystitis, lysolecithin was identified in gall bladder as well as in hepatic bile. However, the most common known organism in bile, in biliary tree disease, is E. coli[52] which is unable to deconjugate bile salts. On the other hand, E. coli infected bile introduced under low pressure in the pancreatic ducts of cats had pronounced mucolytic and cytotoxic effects.[53]

Weiner and his associates[50] have shown that in dogs lymphatic communications do exist between the biliary tract and the pancreas. When acute cholecystitis was produced, by staphylococcal toxin injected into the gall bladder lymphatics or by lipase injected into the gall bladder, acute pancreatitis developed in a high proportion of animals. Furthermore, when india ink was infused into the lymphatics of the gall bladder, it entered the lymphatics in the interlobular spaces of the pancreas. Conversely, india ink infused into the pancreatic lymphatics by ductal injection was demonstrated in lymphatics along the common bile duct.

Dixon and Hillam[54] pointed out that any speculation concerning the mechanism of acute pancreatitis associated with biliary tract disease should explain pancreatitis occuring with cholesterosis of the gall bladder, acalculous cholecystitis, acute and chronic calculous cholecystitis and choledocholithiasis with and without a "common channel." These investigations advanced the following three interesting possibilities: (a) a common underlying factor may be present in biliary tract disease and pancreatitis; (b) biliary tree disease may cause pancreatitis and (c) pancreatitis may cause biliary tree disease.

It is obvious from the preceding considerations that additional studies are required in order to identify the intricate mechanisms involved in this association, such as the role of bile salt deconjugating bacteria—for example, bacteroides, clostridia and streptococcus fecalis. It is possible that bacterial toxins from the biliary tree could find access to the pancreas through anastomotic lymphatic channels and could produce pancreatitis by labilizing cellular membranes with resultant release of pancreatic hydrolases, intracellular as well as exportable.

Hereditary Pancreatitis

Hereditary pancreatitis is a rare condition that manifests itself in childhood, in about half of the patients, and is inherited as a non-sex-linked Mendelian dominant, but poor penetrance of the gene and incomplete recessiveness have not been excluded. All patients have been white and most of them of northern European ancestry. In their patients with familial pancreatitis, Gross and his associates[55] found daily excretions as high as 1,600 mg of lysine and 848 mg of cystine and suggested that this specific aminoaciduria might represent a genetic defect or some other inborn metabolic error. However, aminoaciduria might be seen in some patients with non-familial pancreatitis and might be absent in half of the patients with the familial form. In the latter case the disease should be suspected when blood relatives have similar attacks of abdominal pain, in the absence of biliary tract disease or alcoholism and when there is a history of attacks beginning in childhood. In about half of the reported cases calcification of the pancreas has been found to occur in the larger pancreatic ducts[56,57] as gross calculi. Overt diabetes mellitus and exocrine insufficiency have been found in 20 to 25 percent of cases. The nature of the inherited predisposing abnormality remains unknown, and to date no other defect common to all affected persons has been recognized. Carcinoma of the pancreas has been reported to occur in some cases of hereditary pancreatitis.[58]

Postoperative Pancreatitis

Acute pancreatitis is a well recognized postoperative complication, mainly after biliary and gastric surgical operation although at times it occurs after operations in areas remote from the pancreas—for example, thyroidectomy or transurethral prostatectomy or orthopedic operations.[59] Contributing etiologic factors are trauma to the pancreatic tissue and ducts, and duct obstruction or compromise of blood supply producing ischemia with resultant autodigestion. In instances where local trauma cannot be responsible, hypovolemic shock,[60] the formation of microthrombi and a decrease of trypsin inhibitor in pancreatic juice have been cited as predisposing factors. The highest reported mortality in postoperative pancreatitis is 74 percent.[61] In a series of cases of pancreatitis following biliary tract operations, reported by Bardenheier and his associates,[62] common bile duct exploration and previous history of pancreatitis were considered the main contributory factors. The early postoperative diagnosis of pancreatitis is frequently difficult, and hypotension, oliguria, jaundice or a palpable mass in the upper abdomen, coupled with elevated serum and urinary amylase, should be helpful. With operative injury to the pancreas the amount of amylase in the urine increases, according to Ambromovage et al,[63] and the increment appears to be related more to the functional state of the gland than to the magnitude of pancreatic injury. Keighley and his associates[64] indicated that damage to the sphincter of Oddi in traumatic explorations of the common bile duct and sphincterotomy appear to be the most important factors for postoperative hyperamylasemia and pancreatitis.

Several recent reports of acute pancreatitis following extracorporeal circulation have appeared.[65-67] Johnson and Nabseth[68] reported a case of hemorrhagic pancreatitis following a cadaver renal transplant. Their survey of 1,321 renal transplants showed 23 cases of pancreatitis with 12 deaths. Speculated etiologic factors have been corticosteroid therapy, surgical trauma, induced auto-immune pancreatic rejection, decreased host protective responses and infection.

Pancreatitis in Pregnancy

The reason for the known tendency of acute pancreatitis of pregnancy to develop mostly during the last trimester or in the early postpartum period is obscure. Biochemical, hormonal and mechanical changes occurring during pregnancy and early puerperium might be important. To date, 106 cases of acute pancreatitis have been reported in association with pregnancy.[69] Biliary tract disease has been found in a substantial number of the cases.[70,71] Fatal hemorrhagic pancreatitis in pregnancy attributed to chlorothiazide administration has been reported,[73] and hyperparathyroidism in pregnancy has also been known to be a contributing factor. Maternal hyperparathyroidism leading to suppression of fetal parathyroid glands with resultant tetany in the child is known to occur.[73] Maternal mortality of 24.3 percent in 37 cases observed since 1951 was found by Berk et al.[69] Fetal mortality has also been high. Culdocentesis may be of special diagnostic value in pregnant women. The treatment is generally conservative, with termination of pregnancy to be considered when response to therapy is not satisfactory.

Drug-induced Pancreatitis

New cases of acute pancreatitis have been reported developing in the course of treatment with various therapeutic agents such as corticosteroids,[74,75] agents producing necrotizing angiitis in various organs including the pancreas,[76] salicylazosulfapyridine[77] and thiazides.[78] Acute pancreatitis in patients with acute leukemia and lymphoma during treatment with L-asparaginase (obtained from both A and B strains of E. coli), has been recorded.[79,80] L-asparaginase is known to arrest DNA synthesis and mitosis, in regenerating rat liver and abnormal liver function tests are common during L-asparaginase therapy in man. The mechanism of this kind of acute pancreatitis in man, however, has not been elucidated.

Generalized Infections

Acute pancreatitis has been associated with inflamatory processes through (a) lymphatic propagation from adjacent structures such as the gall bladder, (b) direct extension as in peritonitis, and (c) diseases in which another mechanism, possibly hematogenous spread, has to be considered. Examples of acute pancreatitis occurring in the course of severe bacterial infections have been recorded in typhoid fever, salmonella typhimurium infection,[81] scarlet fever,[82] streptococcal food poisoning,[83] and dysentery.[84] Furthermore, viral infections known to cause pancreatitis in man include viral hepatitis,[85] infectious mononucleosis[86] and mumps.[87] Acute pancreatitis has also been observed in animals infected with the encephalomyocarditis,[88] coxsackie group B[89] and foot and mouth disease viruses.[90]

Miscellaneous

Acute pancreatitis has been found to be associated with a multiplicity of other conditions such as systemic lupus erythematosus, electric shock,[91] methyl alcohol poisoning and atheromatous embolization to the intrapancreatic arteries,[92] to name but a few. In Trinidad, the most common cause of acute pancreatitis seems to be the sting of a scorpion.[93] Of particular interest is a recent series of 26 cases of pancreatic carcinoma associated with acute pancreatitis.[94] Obstructive lesions at the sphincter of Oddi cited recently as a cause of pancreatitis include benign polyps,[95] and regional enteritis of the duodenum.[96]

Despite the large number of known etiologic factors in acute pancreatitis, a group remains without a known cause—the idiopathic group. This group constitutes a variable proportion in the various reported series.

Diagnosis and Differential Diagnosis

Acute pancreatitis is a disease of variable intensity, and for many decades two types have been recognized: the edematous or interstitial and the hemorrhagic or necrotic. In most cases acute pancreatitis is associated with biliary tree disease or alcoholism. Acute alcoholic pancreatitis is usually seen in male patients 25 to 65 years of age who have been drinking heavily for five to ten years. There is no characteristic clinical picture in acute pancreatitis and the manifestations may vary from a bout of vague dyspepsia, with slight abdominal pain, to a fulminating collapse with shock and death. More often than not, the outstanding symptom will be steady, severe epigastric pain, frequently radiating to the back. The most important laboratory test is an elevated serum and urinary α-amylase. In acute pancreatitis, the serum amylase is elevated within two to twelve hours of onset. If there is no rise within 24 hours, the diagnosis probably is not acute pancreatitis. The timed two-hour urinary amylase appears to be a better test because it remains elevated after the serum amylase has returned to normal, usually within two to three days. Recently, an entirely new approach to the assay of amylase has been developed using an insoluble starch labeled covalently with Remazolbrilliant blue and other dyes.[97-100] Two of the methods utilizing the new starch substrates have been automated.[101,102] These new assays have been shown to be simple and rapid and the results highly reproducible. They are considered much superior to the saccharogenic or turbidimetric methods. Whereas it is known that no relation exists between the severity of pancreatic inflammation and the degree of serum amylase elevation, the fact that serum amylase might not be elevated at the time of admission is perpetually ignored, and the assays of urinary amylase are neglected. Such omissions lead to faulty evaluations of the value of amylase determinations in the differential diagnosis of acute pancreatitis.[103] Recent studies have shown that the renal clearance of amylase increases in acute pancreatitis.[104-106] If acute pancreatitis is suspected and serum amylase has returned to normal, determination of the ratio of amylase clearance to simultaneously assayed creatinine clearance might have some value in supporting the diagnosis of pancreatitis. However, an increased serum lipase and two-hour urinary amylase level offer a reasonably accurate diagnosis.[107] Measurements of serum lipase activity have not been widely used because of the long incubation times involved, the instability of the substrates and the technical difficulties of the available methods. A suitable lipase assay must be rapid and must utilize a substrate that is stable, specific for lipase of pancreatic origin and is hydrolyzed to yield a product that can be easily measured. In a recently introduced rapid, automated specific assay method for lipase, monodecanoyl fluorescein is used as substrate.[108] Serum levels of lecithinase A and deoxyribonuclease activity have been found to be elevated in acute pancreatitis but determination of these factors has not gained wide use. Since trypsin and chymotrypsin are exclusively found in the pancreas, the assay of increased trypsin and chymotrypsin in serum should be specific for the distinction of acute pancreatitis from other diseases. However, chemical methods introduced for the assay of trypsin or chymotrypsin in serum are unsuitable for this purpose because of the lack of substrate specificity, lack of sensitivity and the presence of protease inhibitors.

A radioimmunoassay technique has now been developed for the determination of α-chymotrypsin in bovine and human serum,[9] which seems to obviate the difficulties which are inherent to the chemical methods. With this technique a threefold increase in serum chymotrypsin levels was found in patients with acute pancreatitis as compared with normal individuals. Further work is needed, however, for complete evaluation of the usefulness of this immunoassay method in the diagnosis of pancreatitis.

The differential diagnosis of acute edematous or interstitial, from hemorrhagic pancreatitis is significant in prognosis and therapy. The early detection of methemalbumin (0-24 hours) in serum of patients with hemorrhagic pancreatitis, in the presence of haptoglobin, has been suggested for this purpose. This test has been unduly discredited by recent reports.[109,110] Whereas, pancreatic enzymes, mainly trypsin, lipase and elastase can convert hemoglobin into hematin *in vitro,*[111] it seems that tissue enzymes might be also effective *in vivo.* It has been shown that methemalbumin may occur in the serum in several other conditions such as ruptured ectopic pregnancy, severe postoperative intraperitoneal hemorrhage, superior mesenteric artery thrombosis, intrahepatic hematoma, strangulation obstruction and intravascular hemolysis. However, when methemalbumin is detected within the first 24 hours in the serum or in pleural or ascites fluids in a patient with a history and enzyme studies compatible with acute pancreatitis, the diagnosis of the necrotizing form is justified.[112] Plain films of the abdomen have diagnostic value when the "sentinel loop" is present and they also contribute to the differential diagnosis of perforated peptic ulcer or other acute conditions. Additional studies are needed for the evaluation of newer techniques such as the celiac angiogram and the echogram.

Certain Clinical Features and Complications

Pain has always been considered as the main symptom in acute pancreatitis and it is usually epigastric and less often generalized over the whole abdomen. The classic "bandlike" abdominal pain is encountered in a relatively few patients. Only recently, clinicians have realized that at times acute necrotizing pancreatitis may present itself without appreciable pain. Tachycardia, sweating, nausea and vomiting are almost always present. In the course of both interstitial and hemorrhagic pancreatitis large amounts of protein-enzyme rich fluid escape around the pancreas and, in addition to hypovolemia, may cause destruction of nearby tissues.

The complicating features in acute pancreatitis are legion. Stenosing lesions of the colon[113] and colonic fistulization[114] may occur. Mesenteric fat necrosis, producing thrombosis of mesenteric vessels may result in jejunal infarction.[115,116] The urologist should include acute pancreatitis in the differential diagnosis of upper urinary tract lesions, such as changes in the left kidney producing painless hematuria.[117] Rupture of the esophagus[118] and spleen[119] and massive intraperitoneal bleeding due to erosion of the left gastric artery[120] have been reported. Pleuropulmonary complications include basilar atelectasis, pleural effusion, pneumonitis, pulmonary embolus and infarction, empyema and respiratory difficulties due to a pseudocyst formation in the mediastinum.[121,122] A grave complication of pancreatic pseudocysts is bleeding into the cyst[122,124] with subsequent rupture into the stomach, bowel or biliary tree, producing hemobilia and massive upper gastrointestinal hemorrhage.[125] Pseudocysts are relatively rare in childhood and most of the 55 reported cases are due to trauma[126,127] or pancreatitis (mumps). Pseudocysts of the pancreas are so designated because they do not contain an epithelial lining and therefore are not true cysts. The clinical features of pancreatic pseudocysts are highly variable and frequently misinterpreted. Pseudocysts may bleed,[128] erode into adjacent structures,[117,125,129,130] or rupture into the peritoneal cavity, the mediastinum[131] or into the portal vein,[132] or they may cause obstructive jaundice or mimic neoplasm. Individualization of management is required, and is based on location and maturity of the cyst's wall for a safe internal drainage.[133,134]

Perhaps the most serious and least appreciated complications of acute pancreatitis are pancreatic abscesses and lesser omentum collections. They occur in the course or following an attack of pancreatitis, and the causative organism is usually one or more Gram-negative bacteria.[135] In a recently reported series bacterial growth was obtained in 60 of 74 cases.[136] E. coli was seen in 16, Aerobacter aerogenes in nine and Staphylococcus aureus in eight; and more than one organism was present in 30 percent of the cases. External drainage is considered to be the standard procedure in pancreatic abscess, and without surgical intervention the outcome is usually fatal with generalized sepsis.[135,137]

A number of patients with acute pancreatitis have been observed who have become acutely confused during the course of the attack. The patients become very restless, disoriented and difficult to control. The "pancreatic encephalopathy" is most probably caused by the toxic effect of circulating enzymes on the brain[138] and the pathological picture is that of widespread demyelinization and diffuse small hemorrhages in the brain. Central pontine myelinolysis associated with acute pancreatitis has also been reported.[139] Shock complicating acute pancreatitis is an ominous prognostic sign.[140] Its mechanism is at least in part a critical reduction of plasma volume, and oliguria, hyperamylasemia and metabolic acidosis are some of the features. Recent information suggests that the shock of acute pancreatitis should not be considered strictly toxic or strictly hypovolemic. French workers have introduced the term "enzymatic toxemia." Prompt plasma volume replacement favors reversal of the hemodynamic and metabolic deficits in some cases.

Nitrogen retention in acute pancreatitis indicates poor prognosis and the precise mechanism by which pancreatitis impairs renal function is unknown. It is possible that complex vascular and humoral factors are involved.

Pathogenetic Mechanisms Initiating and Propagating Pancreatic Inflammation

Despite the accumulation of a vast amount of experimental data, attemps to relate the several etiologic factors to a single pathogenetic mechanism in acute pancreatic inflammation have failed. A complete review of existing information is beyond the scope of this communication, and only pertinent recent information will be discussed. The pancreas in the average man, weighs about 70 grams (0.1 percent of body weight) and has 13 times the protein-producing capacity of the liver and reticuloendothelial system combined[141] (4 percent of the body weight). Cannulated steer pancreas produces about 1 gram of protein per hour, and 20 percent of the dry weight of the organ constitutes enzyme-protein. With the exception of the mucosa of the gastrointestinal tract, the pancreas is the most rapidly autolyzed body tissue after death.

Normally, the pancreatic proteases and phospholipase A are stored in the exocrine cell as inactive percursors. The ergastoplasm, the Golgi complex, the zymogen granule and the cell membrane proper segregate the exportable pancreatic enzymes in the acinar cell. The same is true for the lysosomal hydrolases which co-exist with the exportable enzymes in the same cell. As an additional safety device against intracellular activation of trypsinogen (the crucial step in the mechanism of zymogen activation) two protease inhibitors are present in the exocrine cell. The interrelationship between lysosomal and exportable enzymes in the biochemical events of acute pancreatitis is not clear. A protease, probably of lysosomal origin, was recently identified in pancreatic secretion with pH optimum between 3 and 5, which is capable of activating trypsinogen into trypsin.[142] Whether such a low pH can be attained in the microenvironment of the exocrine cell is a matter of speculation. The possibility of spontaneous activation of trypsinogen under certain metabolic conditions (hyperparathyroidism, for example) is also possible but requires further documentation.

Proteolytic enzymes have been recovered from pancreatic tissue during the course of experimental pancreatitis,[143] and have been identified in ascites and pleural fluid in acute pancreatitis in man;[7,144] phospholipase A is present in the exudate of experimental pancreatitis[145] in dogs, and chymotrypsin has been detected in the serum of patients with acute pancreatitis.[9] The available evidence strongly suggests that the pathogenetic principle in acute pancreatitis is autodigestion, but the intricate sequence of events remains to be established. Elastase and phospholipase A appear to be significant for coagulation necrosis, vascular injury and hemorrhage. In human pancreatic tissue undergoing necrosis, lysolecithin increased and lecithin decreased, presumably as a result of phospholipase A action.[146] Elastase which has been shown to exist in zymogen form in the acinar cell,[147] appears to play an important role in the destruction of elastic tissue of intrapancreatic vessel walls in hemorrhagic canine[148,149] and human pancreatitis.[150] Recent evidence indicates that under certain conditions a potentiating effect might exist between trypsin and chymotrypsin on elastase as related to elastolysis.[151] Trypsin appears significant in its catalytic action, by activating inactive zymogen, with resultant hydrolytic cleavage of cellular structures, elastolysis and activation of the bradykinin system. Vasoactive polypeptides may account for the glassy edema,[152] and the unduly severe pain in acute pancreatitis. Pancreatic exudate was shown to contain strong kininogenase activity,[152] and could cause hypotension when given intravenously.[153]

Vascular factors in the pathogenesis of acute pancreatitis have received new emphasis in recent reports. In experimental pancreatitis red blood cells have been shown to obstruct lymphatics communicating with pancreatic interstitial spaces,[154] with resultant intensification of the inflammatory reaction. In acute hemorrhagic pancreatitis significant reduction of both pancreatic blood flow and perfusion was found,[155] which would further enhance local ischemia.

Whereas it appears impossible at present to incriminate a single pancreatic enzyme in the pathogenesis of acute pancreatitis in man, the combined action of proteolytic and lipolytic enzymes and of vasoactive polypeptides could explain the histopathologic features and the biochemical consequences of the disease. A plausible, hypothetical, common denominator of the pathogenetic mechanism could be an increase in permeability of cellular lipoprotein membranes surrounding the exportable and lysosimal hydrolases in the acinar cell by variety of factors capable of disturbing cell metabolism and cell membrane structure. Such factors could include endotoxins, exotoxins, viral infections, low pH (acidosis), ischemia-anoxia and direct injury to the pancreas, with resultant initiation of the autocatalytic mechanism.

Metabolic Abnormalities in Acute Pancreatitis

Lipids

The appearance of lactescent serum during an attack of acute pancreatitis is well recognized and is thought to occur in from three to eight percent of cases.[156] It is noteworthy that in pancreatitis with hyperlipemia, serum amylase and lipase values may be normal and it is assumed that gross hyperlipemia interferes with the assay of these enzymes. Thus, urinary amylase determinations are of great value in the diagnosis of pancreatitis in the presence of serum lactescence. It appears that hypocalcemia or tetany or both may complicate acute pancreatitis more frequently when it is associated with hyperlipemia. In a recent series,[157] seven of nineteen patients had hypocalcemia. The syndrome of hyperlipemia that follows pancreatitis is seen most commonly in alcoholics with a type IV lipoprotein electrophoretic pattern, but types I and V have also been reported.

Zieve[158] presented evidence in support of the thesis that hyperlipemia seen in acute pancreatitis results from the liver injury due to alcoholism and malnutrition. A number of other mechanisms have been proposed to explain the hyperlipemia due to acute pancreatitis, among them subclinical defects of lipid metabolism associated with decreased ability to clear circulating triglycerides,[156] transient decrease or inhibition of lipoprotein lipase activity,[159,160] and decreased availability of insulin with resultant defective clearing of dietary lipidemia.[161] However, data concerning plasma insulin levels in acute pancreatitis are scanty,[162] and it would be interesting to know the insulin activity in patients with and without hyperlipemia in the acute phase of the disease. Decreased insulin reserves apparently exist in chonic pancreatitis.[163-165] The difficulties in explaining the hyperlipemia of acute pancreatitis are compounded by the fact that the ingestion of large amounts of alcohol alone can result in moderate triglyceridemia. Ethanol enhances triglyceride synthesis by the liver[166] and the intestine,[167] might decrease lipoprotein lipase activity,[168] and might increase growth hormone and 11-hydroxycorticoid levels[169] in plasma. High levels of plasma cortisol were also found in ten patients with acute pancreatitis and hyperlipidemia.[170] It is known that, in the presence of glucocorticoids, low concentrations of growth hormone stimulate lipolysis, an effect which is said to be mediated by 3′, 5′—cyclic adenosine monophosphate and is blocked by insulin. It is also known that growth hormone and glucocorticoids are involved in the mobilization of fat in animals deprived of food or insulin. Additional work is needed, however, aimed at the clarification of the role of hormonal factors in the pathogenesis of hyperlipidemia associated with acute pancreatitis and alcoholism.

Calcium

Hypocalcemia in the course of acute pancreatitis has been attributed to calcium soap formation in areas of fat necrosis. This theory does not take into account the vast calcium stores in bone, which are rapidly and readily available and can be mobilized within a few hours. Thus, Holland et al[171] showed that serum calcium levels returned to normal in one hour after severe hypocalcemia was induced by infusion of sodium ethylenediamine tetraacetic acid. Large doses of parenterally administered calcium, in patients with acute pancreatitis, often do not raise serum calcium to the expected level. Two additional mechanisms have recently been proposed in order to explain the hypocalcemia of pancreatitis. Increased levels of serum glucagon known to occur during attacks of acute pancreatitis[172] might produce hypocalcemia by stimulating the secretion of thyrocalcitonin with resultant inhibition of bone resorption.[173] It has been shown that glucagon hypocalcemia can be induced in dogs with an intact thyroid but not after thyroidectomy, and *in situ* perfusion of the thyroid with glucagon resulted in a rapid fall of calcium levels.[173] However, despite this suggestive experimental evidence in dogs, glucagon infusion failed to increase serum calcitonin levels in the majority of the normal humans tested.[174] On the other hand, Stern and Bell[175] demonstrated that in tissue culture, using embryonic rat bone labeled with ^{45}Ca, glucagon directly inhibits bone resorption, induced with either parathyroid hormone or dibutyryl-3′-5′-adenosine monophosphate, indicating an additional glucagon action independent of thyrocalcitonin.

Another possible mechanism for the production of hypocalcemia is the concomitant hypomagnesemia,[176] which would make bone refractory to parahormone action.[171] The incidence of hypomagnesemia in acute pancreatitis should be further investigated, especially in cases of the alcoholic variety, the better to assess its role in hypocalcemia. Furthermore, serum glucagon, parahormone and thyrocalcitonin should be determined in a large number of cases of acute pancreatitis, in order to substantiate the significance of hormonal factors in this type of hypocalcemia.

Endocrine Function

During an episode of acute pancreatitis, hyperglycemia and glycosuria develop in a large proportion of patients, and some of them have permanent diabetes following the attack.[178] Whereas injury to the b-cells due to the pancreatic inflammation appears to be the most plausible explanation for this phenomenon, other events such as release of glucagon[179-181] and glucocorticoids[182] might also contribute to the hyperglycemia in acute pancreatitis.

In chronic pancreatitis, the concomitant decrease of a-cell and b-cell function manifests itself by "brittle" pancreatic diabetes. This could also explain the prolonged hypoglycemic response noted in patients with chronic calcific pancreatitis[183] following the intravenous administration of insulin. The effect of glucagon on pancreatic function has been studied in recent years. Administration of glucagon to dogs with pancreatic fistulae depresses the rate of flow, volume and enzyme concentration of pancreatic juice secreted by the pancreozymin/secretin-stimulated gland.[184,185] Similar observations in humans have suggested a possible regulatory role for glucagon in the control of exocrine pancreatic secretion.[186] The possibility has been raised of a compensatory hypersecretion of glucagon in acute pancreatitis, with resultant suppression of pancreatic and gastric secretions and inhibition of gastrointestinal motility. On the basis of these observations, it has been suggested that glucagon might have therapeutic value during an attack of pancreatitis.[187]

Blood Coagulation

Various coagulation abnormalities associated with acute pancreatitis have been described, but diffuse hemorrhage or widespread thrombosis occurs rarely.[188] The most frequent abnormalities are prolongation of the whole clotting time and prothrombin time and a decrease of fibrinogen and factors II, VII and IX with an elevation of the antithrombin titer. The precise mechanism for these abnormalities has not been established. However, the release of pancreatic proteases (for example, trypsin, chymotrypsin and elastase) into the circulation constitutes a plausible explanation of the changes in the clotting mechanism. For instance, trypsin can activate factor X *in vitro,*[189] convert prothrombin into thrombin[190] and digest fibrinogen and other clotting factors. Furthermore, improvement of coagulation variables and correction of hypofibrinogenemia have been demonstrated following the administration of a protease inhibitor from beef lung (Trasylol®)* and epsilon aminocaproic acid.[191] A response to these agents probably indicates an important role for proteolytic enzymes in bringing about coagulation abnormalities in acute pancreatitis. Greipp and his associates[192] observed a patient with acute pancreatitis, complicating the administration of L-asparaginase, and found very low plasma fibrinogen and abundant fibrinogen degradation products in the blood. In a recent experimental study, small doses of trypsin were injected intravenously into rabbits, with resultant rapid decrease of fibrinogen and of platelets.[193] Electronmicroscopic examination of the renal glomeruli showed thrombi containing numerous platelets and fibrin, and light microscopy revealed microthrombi in several organs. Similar phenomena have been observed in experimental[194] and clinical hemorrhagic pancreatitis.

Further studies *in vitro* and *in vivo* are required for a better understanding of the role of various hydrolases, such as trypsin, chymotrypsin, elastase, the phospholipases and the lysosomal enzymes, in the production of coagulation abnormalities in acute pancreatitis.

Treatment

Medical Management

The treatment in acute pancreatitis includes the use of nasogastric suction, analgesics, and the intravenous infusion of colloids and crystalloids, using central venous pressure, hourly urinary output, blood pressure and hematocrit as guides. Colloid loss is replaced with human albumin and with plasma or whole blood. Seriously ill patients will require two to six units of albumin or plasma or whole blood the first 24 hours in order to maintain good peripheral perfusion.[195-197] In cases of hypocalcemia with tetany, intravenous infusion of calcium will alleviate tetany without necessarily restoring serum calcium levels to normal. In the presence of significant hyperglycemia or in cases of acute pancreatitis presenting as hyperosmolar coma, insulin therapy is indicated. Morphine and meperidine (pethidine) are perhaps the two drugs most commonly used for pain of biliary or pancreatic origin, but both produce a decided rise in biliary pressure. Recent evidence suggests that pantazocine is the most appropriate strong analgesic in biliary and pancreatic disease.[198] Anticholinergic preparations have been used in acute pancreatitis in order to suppress gastric and pancreatic secretion, but their effect remains unclear.[199] Their effectiveness in reducing biliary and pancreatic duct pressure is unknown. However, butylscopolamine has been found to produce a pronounced and sustained depressing effect on the morphine-induced pressure elevation in the common bile duct.[200] The usefulness of Trasylol, the protease inhibitor obtained from beef lung, remains unproved and this type of antienzyme therapy has not gained acceptance in this country.[201-203] Intra-arterial infusion directly into the celiac artery did not improve the results in a recent series.[204] Trasylol does not inhibit the elastolytic activity of pancreatic elastase, and has no effect on lipase and phospholipase A. Furthermore, *in vitro* studies have shown that the concentration of this inhibitor sufficient to reduce the activity of a mixture of chymotrypsin and trypsin to a residual baseline reading is not capable of eliminating the potentiating effect of these enzymes on elastase activity. Recent studies with purified human trypsin have shown that this enzyme is not inhibited by soybean trypsin inhibitor and ovomucoid,[205] a fact attributed to possible differences in tertiary structure of the human enzyme as compared with other trypsins. Detailed *in vitro* inhibition studies of all human pancreatic proteases, with naturally occurring and synthetic inhibitors are required. A recent report indicates a beneficial effect in the treatment of acute pancreatitis with a new elastase inhibitor.[206] In cases of acute hemorrhagic pancreatitis the use of peritoneal lavage[207] has been advocated as well as general supportive measures.[208] For a definitive evaluation of peritoneal lavage in hemorrhagic pancreatitis[209] without or with drainage of the thoracic duct,[210] a controlled randomized study in a sizable number of patients is highly desirable. Experimental studies in dogs have shown that agents such as low molecular weight dextran,[211] fibrinolysin or heparin[212] offer considerable protection against the development of hemorrhagic pancreatitis induced by the intraductal injection of trypsin-digested blood. The same was true for animals subjected to postganglionic sympathectomy.[213]

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*Not available on the commercial drug market in the United States.

The prophylactic use of antibiotics for the prevention of secondary infection in severe cases of acute pancreatitis is purely empirical at this point and no controlled studies exist in the literature concerning the effectiveness of these agents. However, the theoretical basis for their use is as follows: In acute pancreatic inflamation there is pancreatic and peripancreatic edema due to the exudation of protein-enzyme rich fluid. The peripancreatic edema may spread to the retroperineal space, the mediastinum, the mesentery and other areas. The protein rich exudate, in edematous poorly perfused tissues, is favorable to bacterial growth. Antibiotics are given with the object of providing an effective concentration in this fluid. Superimposed infection constitutes the most lethal late complication in acute pancreatitis and it is difficult to localize. Most pancreatic abscesses contain one or more Gram-negative bacillus and other bacteria. In choosing an antibiotic in acute pancreatitis, one must remember that hepatotoxicity and renal toxicity should be avoided. Every attempt should be made, of course, for identification of the causative microorganism(s) by blood and peritoneal fluid cultures followed by sensitivity tests. We have mainly used ampicillin, but chloramphenicol, gentamycin or cephalothin with or without kanamycin have been used at times, on the basis of positive blood cultures and sensitivity tests, under constant monitoring of urinary output. Whether bowel sterilization techniques could be beneficial in acute pancreatitis, as prophylaxis against infection, is unknown.

Surgical Management

Accurate diagnosis in a patient with severe abdominal pain, tachycardia and shock, especially when seen late in the course of the disease, may be difficult indeed. Earlier reports suggested a high mortality associated with laparotomy in patients with acute pancreatitis. However, many of the deaths occurred in the terminal stage of serious illness. Recent studies indicate a low mortality with early laparotomy.[214,215] Thus, when acute pancreatitis is suspected the patient is treated vigorously for four to six hours and if the diagnosis is in doubt and the patient is deteriorating despite vigorous supportive therapy, exploratory laparotomy is indicated. The literature does not provide a clear answer to the problem of acute pancreatitis associated with biliary tree disease. Patients with gangrene or perforation of the gall bladder or acute suppurative cholangitis require operation whether or not they have hyperamylasemia or pancreatitis.[54] For patients with severe pancreatitis who respond to treatment slowly, definitive biliary tract operation should be delayed from four to six weeks after complete recovery from acute pancreatitis.[216] An upper abdominal mass suspected of being a pseudocyst, especially one that expands suddenly and gives evidence of intra-abdominal leakage, needs surgical intervention. Persistent rising jaundice necessitates surgical decompression of the biliary tree. If at laparotomy, acute hemorrhagic pancreatitis is found, adequate aspiration of the peritoneal cavity should be carried out and large sump drains should be placed around the pancreas.[217] Total pancreatectomy early in necrotizing pancreatitis, as advocated by some investigators, seems overly drastic in view of the extensive local reaction present.[218,219] Should a pancreatic abscess develop, with spiking fever, high leukocyte counts and evidence of intraabdominal sepsis, surgical drainage is imperative. The nonalcoholic patient presenting with severe pancreatitis and no evidece of acute cholecystitis constitutes a difficult problem. Choledocholithiasis, at the lower end of the common bile duct, is the commonest biliary lesion found in such cases. The treatment is initially conservative, with the patient observed for signs of resolution of the acute attack, and an operation is undertaken later for removal of the stones.

The mortality rate for acute hemorrhagic pancreatitis remains high, especially when renal impairment and azotemia are present. Edematous pancreatitis has a low mortality, except when delirium tremens is present concomitantly. In hemorrhagic pancreatitis the extent of necrosis, and in both the hemorrhagic and edematous forms coexisting disorders such as fatty liver, myocardiopathy and renal disease, constitute important factors affecting the prognosis in the individual patient.

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POST-INTUBATION TRACHEAL STENOSIS

Once patients with post-intubation tracheal stenosis begin to develop symptoms, they are awfully close to obstruction. We have found in patients who are still sedentary from the disease that originally required their respiratory therapy that their airway gets down to about 5 mm before they begin to have symptoms. One of the people in our medical pulmonary unit has done some experiments with volunteers and also measured patients and found that until the airway gets down to the critical diameter of 5 to 6 mm patients at rest really don't have symptoms. This is sort of startling but it is a fact. Most of the patients we have seen have had about the same cutoff point when their condition became obvious or they became totally obstructed.

—Hermes C. Grillo, M.D., Boston

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MEDICAL STAFF CONFERENCE

Combinations of Antimicrobials

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* We are very pleased to have Dr. Ernest Jawetz with us today to discuss the rationale for the use of combination of antibiotics.

DR. JAWETZ:† On the whole, physicians are well satisfied with the position of antimicrobial drugs. They derive a feeling of security from the fact that a majority of microbial infections can be treated effectively and cheaply and that most patients recover not only from the infection but also from the undesirable effects of the drugs. However, from time to time, the physician's feeling of security is threatened. He hears about the emergence of drug resistance, about superinfections, about failures of antimicrobial drug treatment. At such times he wonders: If one drug is good, might two not be better, and might three not cure every patient of every disorder? Such sentiments are undoubtedly involved in the very widespread use of antimicrobial combinations. For example, 11 percent of 7,094 patients admitted to Johns Hopkins Hospital during a three-month period in 1963 received from two to five antibiotics, whereas only an additional 7 percent received a single antibiotic. Some years ago a correspondent, surveying the German drug market, found hundreds of preparations containing several drugs and concluded: "It has become unfashionable to use one drug by itself."[1,2]

Even if we acknowledge the vast abuse of drug mixtures, some reasonable indications for the use of antimicrobials in combinations may be listed briefly:

1. Prompt treatment of a desperately ill patient who is suspected of having a serious infection. Two or more drugs are aimed at the several most likely pathogens. The commonest example at present is the initial treatment of suspected Gram-negative bacterial sepsis. Commonly employed combinations "aimed" at the most serious organisms consist of gentamicin plus carbenicillin, or kanamycin plus cephalothin or ampicillin.
2. The emergence of microbial mutants resistant to one drug may be greatly delayed by the simultaneous presence of a non-cross reacting second drug. This applies particularly to chronic infections—for example, tuberculosis where simultaneous use of two drugs, or even three drugs, is universally accepted to deal with large microbial populations in symptomatic disease.
3. Mixed infections—for example, in the respiratory tract—usually are well managed with a single drug. Very rarely, however, simultaneous sepsis with two organisms may require the use of two drugs, each aimed at one organism.

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4. The desire to achieve bactericidal synergism is a much advertised claim and a fervent desire —but very rare in reality. It is discussed below.

In contract to the above list of possible clinical indications for antimicrobial combinations, there is a longer list of disadvantages of their use:

1. If a physician already administers penicillin, kanamycin, erythromycin, tetracycline, cephalothin, vancomycin—and a dash of cortisone—to a very sick patient, he feels that everything possible is being done for that patient. This gives the physician a false sense of security, and he will not expend all possible effort toward a specific diagnosis which might permit specific treatment. The result is direct harm to the patient.
2. The more antimicrobials given simultaneously, the greater the chance for sensitization of the patient, or for adverse reactions, be they toxic or hypersensitive.
3. Unnecessarily high cost.
4. All too frequently a drug combination achieves no greater therapeutic benefit than a properly selected, effective single drug.
5. "Fixed" antimicrobial combinations are always unsuitable for specific treatment; usually there is too high a dose of one drug and too low a dose of the other drug. This and many other reasons have led to the recent disapproval of fixed antimicrobial combinations by regulatory agencies in the United States.

Let us now review the types of combined drug effects which might occur if two antimicrobials act simultaneously on a homogeneous microbial population (Chart 1). By far the commonest situation is that drug A has very little effect, and drug B is moderately effective in reducing the number of viable microorganisms. A plus B is similar to B (the more active drug) alone. This type might be called "indifference of drug interaction," and it occurs in a large majority of clinical situations where two antimicrobials are employed together—a striking waste.

The most desirable interaction might be called "synergism": Drug A alone has very little effect, drug B inhibits growth moderately, but—through some magic—A plus B produces rapid killing of the entire microbial population. Such "synergism" unfortunately is very rare, and it is entirely specific for a given drug combination, acting on a single strain of microbes.

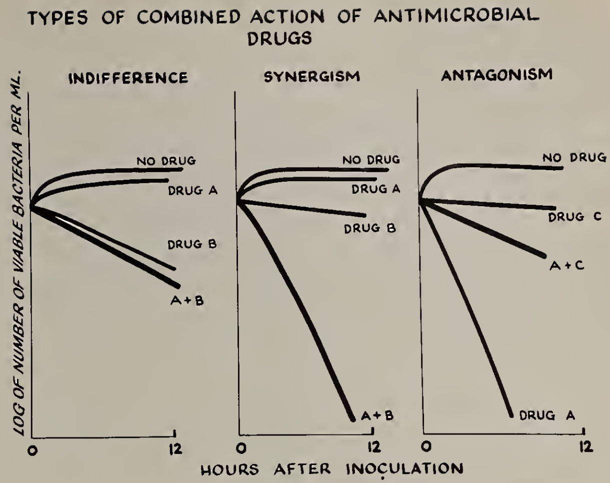

Chart 1.—Types of combined action of two antimicrobial drugs on a homogeneous microbial population. Schematic representation of bactericidal action *in vitro*, showing the possible types of results seen when one drug, or two drugs, act on a homogeneous population of bacteria, under conditions permitting growth.

The third possibility is that drug A alone is significantly bactericidal against an organism, while drug C alone has a barely inhibitory effect. The addition of C to A results in a pronounced reduction of the antibacterial efficacy of A. This can be called "antagonism." A few characteristics of antimicrobial antagonism are worth noting. *In vitro* antagonism is observed most readily as a reduction in the rate of bactericidal action when two drugs are acting simultaneously on a homogeneous microbial population. In experimental infections (Chart 2), this antagonism can also be demonstrated when a primarily bacteriostatic agent (for example, chloramphenicol, tetracycline, sulfonamide) in a barely effective amount is administered before, or with, a minimal therapeutic dose of a bactericidal agent (for example, a penicillin, an aminoglycoside). However, the antagonism can be overcome readily by an excess of the bactericidal drug (Chart 2). The mechanism of antagonism is not fully understood, but it apparently depends on a pronounced slowing of microbial metabolism by the "antagonizing" drug (for example, an inhibitor of protein synthesis) before the action of the bactericidal drug (for example, an inhibitor of cell wall synthesis) if the latter depends on active microbial metabolism for optimal action. The experimental demonstration of antimicrobial antagonism *in vitro* and *in vivo* is interesting—but does antagonism ever occur in clinical treatment of human infections? It can occur under special circumstances. The best known examples

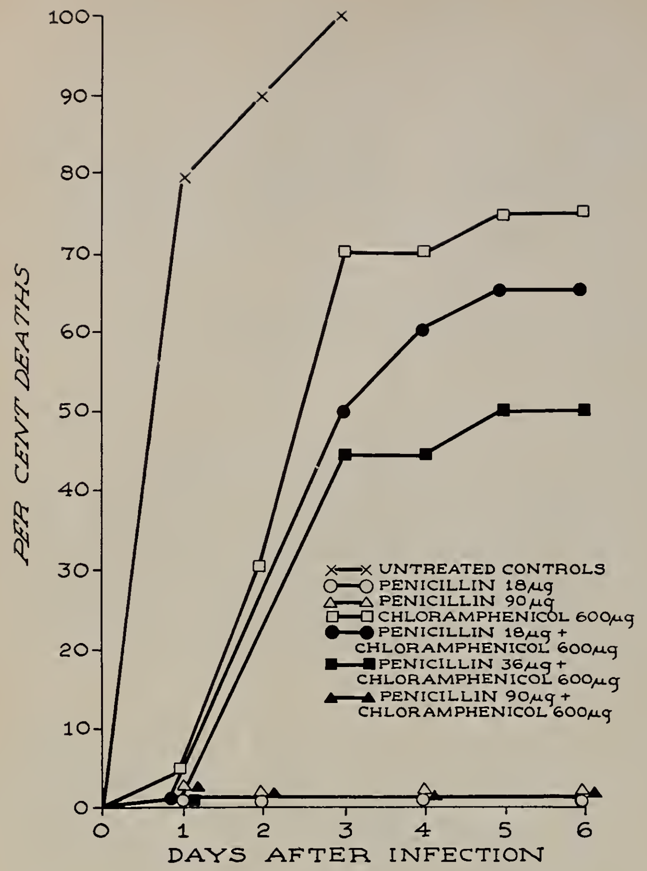

Chart 2.—Death rates observed in a streptococcal infection of mice treated with penicillin alone (18 or 90 µg per mouse), chloramphenicol alone (600 µg per mouse), or penicillin in various doses administered at the same time as chloramphenicol, but injected separately. While chloramphenicol antagonizes the action of penicillin, an excess of penicillin can overcome this antagonism.

come from the treatment of bacterial meningitis. Twenty years ago Lepper and Dowling[3] showed that in the treatment of pneumococcus meningitis the addition of chlortetracycline to full therapeutic doses of penicillin decidedly increased the mortality (Table 1). More recently Mathies et al[4] had a similar experience with the addition of chloramphenicol to therapeutic doses of ampicillin in bacterial meningitis of children (Table 2). While antimicrobial antagonism thus *can* occur in clinical therapy (the literature contains several other examples), I believe that it is so limited by time-dose relationships (see above) as to be an unlikely and rare outcome in the treatment of human infections.

The possibility of achieving synergistic effects deserves detailed discussion. At least three mechanisms for antimicrobial synergism are known.[5]

TABLE 1.—*Clinical antibiotic antagonism. Treatment of pneumococcus meningitis**

	No. of Patients	*Deaths*	
		No.	*Percent*
Penicillin 12 million units i.m. daily X 14	43	13	30
Penicillin, same dose + chlortetracycline, 50 mg per kg per day i.v.	14	11	79

*Cases of comparable stage and severity.[3]

TABLE 2.—*Ampicillin in bacterial meningitis*[4]

Drugs Used	*No. of Patients*	*Deaths*	
		No.	*Percent*
Ampicillin 150 mg per kg per day 10-12 days	140	6	4.3
Ampicillin 150 per mg per kg per day + chloramphenicol 100 mg per kg per day + streptomycin (2 days)	124	13	10.5

1. *Blocking successive steps in a metabolic sequence.* Sulfonamides are antibacterial because they compete with para-amino-benzoic acid which is required by some bacteria for the synthesis of dihydrofolate. Folate antagonists (for example, trimethoprim, pyrimethamine) inhibit the activity of the enzyme which reduces dihydrofolate to tetrahydrofolate (dihydrofolic acid reductase). These folate antagonists inhibit bacterial and protozoal enzyme thousands of times more efficiently than the enzyme of mammalian cells. The simultaneous presence of a sulfonamide and a folate antagonist results in the simultaneous block of sequential steps in the pathway, leading to the synthesis of purines and nucleic acid (Chart 3). Such a simultaneous block can result in much more complete inhibition of growth than the action of either component alone. Optimal proportions of the components of the mixture have been estimated *in vitro,* but may be difficult to maintain *in vivo.* This type of "synergistic," combined antimicrobial action is being applied to urinary tract infections, enteric fevers, malaria, and toxoplasmosis.[6]

2. *Inhibition by one drug of an enzyme which can destroy the second drug.* Penicillins suscep-

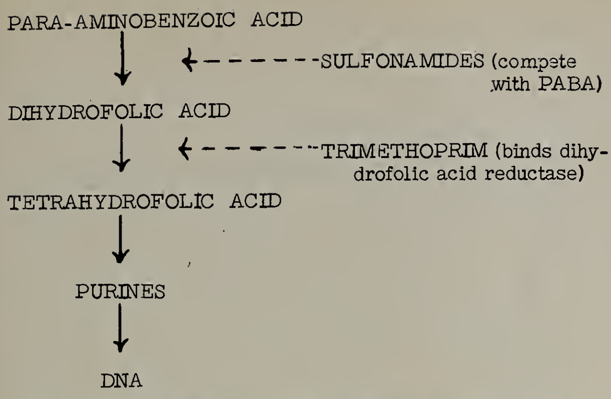
PARA-AMINOBENZOIC ACID
SULFONAMIDES (compete with PABA)
DIHYDROFOLIC ACID
TRIMETHOPRIM (binds dihydrofolic acid reductase)
TETRAHYDROFOLIC ACID
PURINES
DNA

Chart 3.—Mechanism of the synergistic action of a sulfonamide and a folate antagonist.

tible to destruction of beta-lactamases (penicillinases) are usually ineffective against organisms which produce such lactamases. However, if the lactamase of an organism could be firmly bound, then penicillins might be effective against this organism. Certain lactamase-resistant penicillins and cephalosporins have a much higher affinity for some lactamases than do hydrolyzable penicillins (for example, penicillin G, ampicillin). Lactamases from pseudomonas and other Gram-negative bacteria are bound very efficiently by methicillin, cloxacillin or cephalosporins. These drugs are resistant to lactamase action and can protect hydrolyzable penicillins from destruction. This type of synergistic effect has been employed a few times in clinical therapy,[7] but sufficient concentrations of the binding drugs are easily achieved only in urine, not in the systemic circulation.

3. *Synergism manifested by pronounced enhancement of early bactericidal rate.* This type of combined antimicrobial action has been studied extensively and reviewed repeatedly.[5,8] Some of its characteristics are as follows: The effect extends over a fairly wide range of concentrations of each member of the drug pair; only one member of the pair need exhibit antimicrobial activity alone in the concentration employed in the mixture; the other member may be ineffective in that concentration, although active against the particular organism in a 10-fold to 1000-fold higher concentration.

This type of synergism has been demonstrated with Gram-negative bacteria, staphylococci and other organisms, but it has been studied in greatest detail with enterococci (Streptococcus fecalis). Most enterococci are inhibited, but not killed, by penicillins.[8,9] The addition of an aminoglycoside (streptomycin, kanamycin, gentamicin) in amounts achievable in the systemic circulation results in an immediate, striking increase in the rate of bactericidal action, although that concentration of aminoglycoside alone has no discernible effect *in vitro.* Enormous concentrations of a given aminoglycoside (for example, streptomycin 6 mg per ml, kanamycin 3.7 mg per ml) are inhibitory to the enterococcus *in vitro,* unless the particular strain is genetically resistant. In the latter case there will be no synergism when that particular aminoglycoside is added to a penicillin.[10,11] The mechanism of this type of synergism probably depends on the ability of drugs which inhibit cell wall synthesis (for example, penicillin) to greatly enhance the permeability of enterococci to aminoglycosides, so that the latter can exert a lethal action on the ribosomes of the bacteria. The uptake of radioactive aminoglycosides is greatly enhanced in enterococci by penicillins, but not by drugs which affect cell membranes, or protein synthesis.[12] However, cephalosporins do not readily participate in this synergistic effect with aminoglycosides.

Enterococci (Streptococcus fecalis) are the etiological organisms in 5 to 15 percent of cases of bacterial endocarditis. Treatment with penicillin alone fails to cure a majority of patients with enterococcal endocarditis,[9,13] and only a few patients have been treated and cured with ampicillin alone. By contrast, penicillin combined with an aminoglycoside has frequently eradicated the infection. In the past, most commonly, penicillin was given together with streptomycin or kanamycin.[13,14] More recently, some strains have appeared to be completely resistant to huge concentrations of these aminoglycosides,[10,11,15] but still susceptible to a combination of penicillin with gentamicin.[16]

Synergistic combinations of carbenicillin with gentamicin have been employed in pseudomonas sepsis of immunodeficient leukemic patients.[17] Other types of Gram-negative sepsis may also be susceptible to "synergistic" drug action [18,19] if a specific drug combination can be selected by laboratory means for a specific infecting organism. Before the advent of specific anti-staphylococcal penicillinase-resistant drugs (for example, methicillin, vancomycin) cases of staphylococcal endocarditis could often be cured by specifically selected synergistic drug combinations.[20] In many other claims for the clinical efficacy of "synergistic" antimicrobial combinations, there are serious doubts regarding the validity of the evidence on which the claim is based.

Conclusion

Perhaps because of its large financial impact, the field of combined antimicrobial drug action has been filled with intense emotions, violent claims and counterclaims. An effort was made in this brief summary to describe the simplest common denominators which determine combined antimicrobial activity in the laboratory and in its application to clinical treatment. A famous physician, Moses ben Maimon, is said to have written 800 years ago: "If one can manage well with one individual drug, one should not use a compound one. . . . One should use medications compounded of multiple ingredients only when compelled to do so."[21] I may express the pious hope that my brief presentation may help physicians feel compelled less often to use combinations of antimicrobial drugs.

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FLUID REPLACEMENT IN BURNED PATIENTS

In our studies on fluid replacement in burn patients, I think one thing stands out: The rapidity of fluid loss is much faster than we have been led to believe by replacing fluids according to clinical signs. In essence our studies really show that the majority, if not all, of the fluid sequestration into the burned area is in the first 24 hours. By using a 48-hour period of fluid replacement, we are playing "catch-up." So we attempt, and have been for the last several years, to give the entire quantity in 24 hours, with quite beneficial results. I think also that it's less important what particular solution you choose as long as you give enough of it and fast enough.

—Basil A. Pruitt, Jr., Ft. Sam Houston

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Important Advances in Clinical Medicine

Epitomes of Progress -- Pediatrics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Pediatrics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Synthesized Releasing Hormones

During the early 1940's it was suggested that hypothalamic control over the release of anterior pituitary hormones was exerted by substances secreted into the hypothalamo-hypophyseal portal vessels. Some of these agents or releasing factors have since been isolated. A major recent advance in endocrinology has been the isolation, determination of structure, and synthesis of thyrotropin releasing hormone (TRH), a tripeptide, by Guillemin and by Schally, and luteinizing hormone-releasing hormone (LH-RH), a decapeptide, by Schally and his co-workers. The availability of synthesized releasing hormones has made it possible to further investigate anterior pituitary function, and it has been shown that the administration of TRH results in increased levels of serum prolactin, as well as thyroid stimulating hormone (TSH) in man. LH-RH administration causes increased release of luteinizing hormone and follicle stimulating hormone in man. These studies indicate that releasing hormones may have similar or identical structures, suggesting that anterior pituitary cells may exhibit varying responses to stimulation at different times, which may account for secretion of different trophic hormones. It has been shown that when TRH is given to hypopituitary children, increased TSH release occurs in some, indicating that the primary deficiency may be at the hypothalamic level and that such patients do not have primary hypopituitarism. The availability of synthetic releasing hormones may be expected to open new avenues in the investigation of control of anterior pituitary function and may provide agents useful in the treatment of tropin-deficient patients. Mass production of these synthetic agents is of course far more practical than the synthesis of pituitary peptide hormones, and it is possible that oral administration of the former may be effective; for example, oral administration of TRH has been shown to be effective in experimental animals. Moreover, antibody formation in response to the administration of the releasing hormones is much less likely to occur.

BAGHER M. SHEIKHOLISLAM, M.D.

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Costom B, Grumbach M, Kaplan S: Effect of thyrotropin-releasing factor on serum thyroid-stimulating hormone—An approach to distinguishing hypothalamic from pituitary forms of idiopathic hypopituitary dwarfism. J Clin Invest 50:2219-2225, Oct 1971

Jacobs L, Snyder P, Wilber J, et al: Increased serum prolactin after administration of synthetic thyrotropin releasing hormone (TRH) in man. J Clin Endocr 33:996-998, Dec 1971

Acute Cerebellar Encephalopathy as a Remote Complication of Neuroblastoma

Diagnostic considerations for a sick child who suddenly becomes very ataxic always include drug intoxication, encephalitis and brain tumor. Less common is the sudden development, in an infant or young child, of wild, chaotic, nystagmoid eye movements, irritability and diffuse clonic muscle activity in the extremities (with normal electroencephalogram). This disorder appears in the literature under various descriptive headings including opsoclonus, acute cerebellar ataxia, pontine encephalitis, myoclonic encephalopathy of infancy, ataxic conjugate movements of the eyes or the syndrome of "dancing eyes and dancing feet." We prefer the term *acute cerebellar encephalopathy,* because most of the patients we have seen with the disorder have persistent dementia even though the ataxic movement disorder is the most prominent early sign.

Etiologic factors may be variable, but it has become clear that a significant association exists between this distinctive encephalopathy and a neuroblastoma which is often inapparent. The tumor may arise anywhere along the paraspinal sympathetic ganglia including the adrenal gland. Autopsy studies of a few patients have revealed findings which are consistent in location but variable in severity—atrophy of cerebellar cortex, especially Purkinje cells and loss of nerve cells from the dentate nucleus. What the interrelationship is between a silent neuroblastoma and remote damage to the brain is not clear.

From a practical standpoint, patients who present with this neurologic syndrome should be surveyed carefully for an inapparent neuroblastoma because it is one of the commoner malignant lesions of childhood and the cure rate is unusually high, especially in young children who are treated intensively. The clinical and laboratory survey should include (1) chest and skeletal x-rays, (2) intravenous urogram, (3) quantitative determination of urinary VMA, and (4) a bone marrow examination for malignant cells.

PATRICK F. BRAY, M.D.

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Salt Poisoning from Saline Emetics

Hypertonic solutions of sodium prepared with common table salt or baking soda have been recommended for induction of emesis in the management of poisoning and overdose, appearing on product labels, in first aid manuals, and in the poison control and pediatric literature.

Iatrogenic salt poisoning is being reported more frequently as a consequence of these recommendations and after gastric lavage with hypertonic sodium solutions and, intra-amniotic injections of hypertonic sodium solutions for the induction of abortions. Home prepared electrolyte solutions prescribed for the management of gastroenteritis are another source of frequent accidental salt poisoning.

Hypernatremia as a consequence of salt ingestion may be accompanied by dehydration, but the total body sodium in these cases is generally elevated. This is in contradistinction to hypernatremic dehydration from other causes, where there is usually a total body deficit of sodium, and a deficit of water in excess of the deficit in sodium. In the former case, the treatment, to remove the excess sodium as rapidly as possible. This may be achieved most effectively by dialysis procedures.

Salt solutions have not been demonstrated to be reliable emetics and use of them may delay more effective measures. The recommendations for the use of salt solutions as an emetic should be deleted from instructions. Where emesis is indicated, other safer and more effective agents, such as syrup of ipecac, should be employed.

Frank DeGenaro, m.d.

REFERENCE

DeGenaro F, Nylan WL· Salt—A dangerous "antidote." J Pediatr 78:1048-1049, Jun 1971

Interhospital Infant Transport

Experience has indicated that specialized equipment operated by adequately-trained personnel is necessary when transferring critically ill infants between hospitals to avoid increased risk to the patient. Personnel should include a neonatologist, perinatal nurse, vehicle operator, and other physician staff and nursing personnel as required for the individual transfer. The ambulance or aircraft must accommodate a portable incubator with good lighting, accessibility, temperature control and humidified oxygen source. Electronic monitoring of heart rate, oxygen centration, and blood pressure is advisable and provision for adequate artificial ventilation should be on hand. A portable infusion pump is used for intravenous or intra-arterial fluid administration.

With use of proper equipment by trained personnel, high speed transfer is rarely necessary as intensive care facilities are available for patient use throughout the transport.

In the future, each hospital offering neonatal intensive care will be expected to develop specialized transport facilities for use with their unit.

Richard L. Thompkins, m.d.

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Segal S: Transfer of a premature or other high-risk newborn infant to a referral hospital. Pediatr Clin North Am 13:1195-1205, Nov 1966

Triple Vaccine

Recently available triple vaccine for measles, rubella and mumps produces protection against each at about 95 percent. This method would appeal to those who wish to reduce the number of injections, visits and expense.

All children should be immunized against measles because of its severity and sequelae. Duration of protection is uncertain but requires such minute amounts of antibody that one might surmise lifetime immunity.

Rubella is a benign disease in childhood and confers permanent immunity. Most artificially induced immunity lapses with time and the duration is uncertain. The only significant purpose for vaccination of infant boys and girls is to protect their mothers from being infected by them with fetal damage during pregnancy. Only 20 percent of mothers are susceptible, the others having had the disease during childhood. Vaccine *may* prevent infection in childhood (natural infection produces permanent immunity) but lapse before child-bearing years. The girl immunized at one year has not been proved to be protected during pregnancy 20 years later.

Mumps is relatively benign in childhood with very rare exceptions and produces permanent immunity. Vaccination at one year will probably protect through childhood but may very well not extend to adult years when orchitis is a serious complication.

Objections to the proposal to give all year-old infants triple vaccine are theoretical and perhaps philosophical. The physician has an individual responsibility to his patients. He may choose to give measles vaccine at one year and to defer rubella, as the British have done, and mumps to pre-adolescent years for better protection at a more important time. Effective immunity to all three components of triple vaccine persist for two and a half to five years, only possibly into adulthood.

EDWARD B. SHAW, M.D.

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Recognition of Serum Hepatitis

The clear association between Australian antigen and serum hepatitis virus establishes methods for identifying the disease. Recently published reports also demonstrate that serum hepatitis virus (currently being named hepatitis B, and contrasting with hepatitis A or infectious hepatitis) may be propagated in the laboratory.

With such means at hand the occurrence of hepatitis B in (1) older age groups, (2) institutional populations, (3) military, (4) drug addicts, (5) those patients requiring blood and blood products, and finally in (6) the immunologically impaired individuals, can be easily recognized.

A number of different methods of detecting hepatitis B have led to recognition of widespread infection with this virus and the realization that blood banks must screen all potential donors, and such screening should utilize the most sensitive detecting systems that will still be simple enough to incorporate into routine laboratory procedures. Comparisons of these methods are being made in a number of laboratories throughout the country. However, more time and effort will be required before any final decisions are rendered. In the meantime, any one of the following methods for detecting serum hepatitis viremia could be used: (1) Double diffusion in agar (1-2 days), (2) complement fixation (2-4 hours), (3) counter immunoelectrophoresis (6 hours), (4) rheophoresis (16-20 hours), (5) isotope immunoassay (18 hours), (6) passive indirect hemagglutination (4 hours).

J. J. QUILLIGAN, M.D.

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Current Dietary Hazards

With the rising interest in "health foods" and fad diets, a comprehensive dietary history is increasingly important as part of the pediatric health evaluation. Until recently it was necessary to journey to an underdeveloped nation to study rickets, scurvy, and kwashiorkor. Now, so-called "macrobiotic" diets have brought about reappearance of the diseases in the United States. Some parents feed their children a diet of only brown rice and seaweed in the quest for a balance between the opposites of "Yin and Yang," with death or serious illness an occasional result.

Along with the re-emergence of deficiency states, hypervitaminosis A and D are being seen with increasing regularity.

JOHN BOLTON, M.D.

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The use and abuse of vitamin A (American Academy of Pediatrics Joint Statement of Committees on Drugs and Nutrition): Pediatrics 48:655-656, Oct 1971

Evaluation for Possible Immunologic Deficiency Disorders

Patients with recurrent infection or infection with unusual microbial agents require evaluation for possible immunologic deficiency. The defect may involve antibody mediated immunity, cell mediated immunity or a combination of both systems.

Antibody mediated immunity may be assayed by quantitating the amount of circulating antibody of the IgG, IgM and IgA class (values should be compared to normals of same age). IgE and IgD require specialized techniques for quantitation. Specific antibody function can be determined following immunization using the Shick test for diphtheria or antibody assay for poliomyelitis, measles, etc.

Cell mediated immunity may be assayed by several means. Lymphopenia (less than 1000 lymphocytes per cu mm at any age) suggests that a deficiency is present. Most individuals with intact cellular immunity will respond to at least one of a battery of antigens (Candida, histoplasmosis, PPD, mumps, streptokinase-streptodornase). If all skin tests are negative, then the peripheral lymphocytes may be tested for function by stimulation with phytohemagglutinin.

Simplified tests are also available for determination of phagocytic capabilities. Many of these use the reduction of a dye (nitrobluetetrazolium) by granulocytes to determine function.

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Assessment of the Risk of the Respiratory Distress Syndrome with Preterm Delivery

Preterm delivery is often associated with inability of the newborn infant to support respiration, resulting in the respiratory distress syndome (RDS), the leading cause of neonatal mortality. Most tests to determine if the fetus is ready for delivery are based on analysis of amniotic fluid for various metabolic products. While these tests correlate roughly with length of gestation, they do not assess the maturity of the lung. This can be predicted by chemical analysis of amniotic fluid for the major component of pulmonary surfactant, the substance deficient in the lungs of infants who develop RDS.

Recently a rapid, simple amniotic fluid surfactant test has been developed which reliably predicts the risk of RDS. Its clinical usefulness should increase as agents for suspending labor and pharmacologically accelerating lung maturation become available.

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The Return of the Scabies Mite

After an absence of almost two decades the itch mite (Sarcoptes scabei) has returned to reside with a sizable portion of the world's population. Children and young adults appear to be especially susceptible, particularly when living under conditions of crowding and poor personal hygiene. The epidemic recurrence of scabies every 15 to 20 years is thought to have an immunologic basis.

Diagnosis is made by finding the body or parts of the body of the tiny (0.35 mm) mite, usually at the end of a burrow. The lesions, some of which may be vesicular, are characteristically found in the interdigital spaces of the fingers, the palms, the wrist flexures, the inner and posterior sides of the elbows, the anterior axillary folds, belt line, buttocks, and the margins of the soles of the feet.

The diagnosis can be easily missed if the lesions are sparse, as they frequently are, or if their appearance is altered by topical steroids, certain irritating medications or by scratching and rubbing.

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Medium Chain Triglycerides in Pediatric Practice

Usual food fats contain long chain fatty acids (LCT), largely C16 and C18. Absorption and digestion of these require emulsification by bile acids, hydrolysis by pancreatic lipase, re-esterification to triglycerides and subsequent incorporation into lipoproteins (chylomicron), which are transported via the lymphatics. Unlike LCT, significant absorption of medium chain triglycerides (MCT) occurs in the absence of bile acids and pancreatic lipase. MCT are C8 and C10 fatty acids found mainly in coconut oil. MCT are helpful mainly in malabsorptive states such as cystic fibrosis and meconium ileus. MCT may improve the nutritional status in patients with massive small bowel resection, and in infants with neonatal hepatitis, biliary atresia or other hepatic disorders. MCT may improve the nutritional state in patients with congenital or acquired lymphatic disorders in childhood and decrease the hyperlipidemia in von Gierke's disease and defective chylomicron formation in a-B-lipoproteinemia. Special milk formulas high in MCT and low in LCT are marketed by Mead Johnson Company as Portagen® and Progestinil®.

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Immunosuppressive Therapy of Renal Disease

Apart from the occasional use of nitrogen mustard and the future use of antilymphocytic globulin, there are three immunosuppressive agents currently used in treating renal disease. First are the corticosteroids all of which including ACTH have the same effect on nephropathies. Second is the purine analogue, azothioprine (Imuran®). Thirdly is the alkylating agent cyclophosphamide (Cytoxan®).

None of the above agents has any role in therapy of usual acute glomerulonephritis, acute renal failure, established chronic nephritis or any form of pyelonephritis. Furthermore, each was found totally ineffective in treating familial nephropathy (Alport's syndrome) and various forms of cystic diseases including nephronophthisis.

In idiopathic nephrotic syndrome, so-called "nil disease" because of the absence of morphologic changes under the light microscope, the treatment of choice is corticosteroids (prednisone). In steroid dependent or steroid resistant nephrosis, cyclophosphamide is the drug of choice.

High-dose continuous steroids for six months is the treatment of choice for lupus nephritis. For patients not responding or unable to tolerate high-dose steroids, azathioprine is the next drug of choice.

An occasional patient with progressive proliferative nephritis may respond favorably to combined corticosteroid and azathioprine therapy.

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Relationship Between Birth Weight And Gestational Age

Today, we appreciate that many infants may represent a deviation of intrauterine growth; that these infants either may be too big or too small for their length of gestation. For example, the infant born to the mother with diabetes is perhaps the best known example of the infant "too large for length of gestation" although there also are infants with Beckwith's syndrome, transposition of the great vessels, and post-term infants who continue to develop because the placenta does not show the normal aging and fibrinous degeneration.

Of the infants who at birth are small for their length of gestation or are *dysmature*—the best known is the twin. Ordinarily, the uterine environment favors only one pregnancy. The presence of two placentae may result in two undersized babies or else one normal sized baby and one markedly small, particularly in identical twins. Twins are representative of those infants who are true *nutritional dysmatures*, where there has been a normal number of cell divisions but whose individual cells are small. This group includes infants born to mothers with toxemia, hypertensive cardiovascular or renal disease, at high altitude or with insufficient placentas. Characteristically these infants are small but normal. They grow rapidly after birth and do well unless there has been a severe chronic problem of anoxia affecting the fetus.

However, another category, the *total growth dysmatures,* include infants born with a variety of genetic diseases (for example, cystic fibrosis, osteogenesis imperfecta), those born with chromosomal problems such as Down's syndrome (mongolism), 17-18 trisomy and 13-15 trisomy; severely malformed infants (for example, primary microcephaly, holoprosencephaly, Cornelia-De-Lange syndrome, etc.) and a major group of infants severely affected due to early invasion of fetal tissues by rubella or cytomegalic inclusion viruses or with toxoplasmosis. These *total growth dysmatures* lack the normal numbers of cells due to fewer cell divisions. Their prognoses, unlike the *nutritional dysmatures* are poor and limited.

The premature infant in the scale of "appropriateness for gestational age" is of normal size for length of gestation and represents an infant born too soon, who was not allowed to stay in utero and enjoy the advantages of intrauterine development.

An additional category is represented by infants known as postmatures, who have been in utero beyond 42 weeks and who have begun to resorb their own tissues, show signs of weight loss but who are of normal length and normal head circumference. These are another form of *nutritional dysmatures.*

Among the major reasons for the awareness of the various types of dysmatures are that the *nutritional dysmature,* with his excellent prognosis should be anticipated as a product of a high risk pregnancy and within the first hours after birth begin to be fed with intravenous glucose-containing infusions. He lacks adequate glycogen reserves in his liver and must be supplemented with glucose very early after birth in order to avoid possible brain damage due to hypoglycemia.

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The Hexachlorophene Controversy

The worldwide acceptance of a hospital nursery routine of daily baths with pHisoHex for all infants (with special care to wash the cord) was followed by virtual elimination of staphylococcal colonization and disease from nurseries.

Recently circumstantial evidence of potential toxicity of hexachlorophene to man has been offered. Edema (reversible) involving myelin sheaths has been found in rats in experiments where rats were fed large amounts of hexachlorophene for long periods. Similar lesions can be induced in monkeys. Blood levels of hexachlorophene in babies washed for 3 to 5 days sometimes were as high as ⅓ to ½ those found in rats with experimental lesions from ingestion of hexachlorophene. No actual toxicity has ever been recognized in millions of washings of newborn infants with pHisoHex carefully rinsed after washing. The recent restrictions by the FDA (and American Academy of Pediatrics) against the use of hexachlorophene cleansers for bathing of newborns was followed since December 15, 1971, by a number of outbreaks of staphylococcal disease in nurseries. Further recommendations (FDA, AAP) were then issued suggesting the use of hexachlorophene bathing of newborns to help control outbreaks.

At the time of this writing it is not known how extensive are the outbreaks. To date there has been established no known toxicity of hexachlorophene bathing for infants. Several studies are under way to reexamine the efficacy of hexachlorophene today and to try to establish whether or not there is toxicity. The FDA, the Center for Disease Control, the American Academy of Pediatrics are all cooperating in trying to assess the various criteria: patterns of disease, short and long-term effects related to staphylococcal colonization and disease, attempts at control by pHisoHex and other measures.

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Diet and Coronary Artery Disease in Children: Facts and Fiction

Does coronary artery disease have its inception in the infant and the young child and should measures to prevent it begin at this time? There is no complete nor definitive answer to this question at present.

Recommendations for dietary modifications have been suggested, notably by the Inter-Society Commission for Heart Disease Resources on the Primary Prevention of Atherosclerotic Disease (Circulation, December 1970). More recently a committee of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association has suggested certain changes in the diet of children, particularly in high risk families in which there is a high incidence of coronary artery disease and occlusion and/or infarct under the age of 50 years, and those in which hyperlipidemia type II has been demonstrated. The Committee on Nutrition of the American Academy of Pediatrics has recently summarized the evidence for relating dietary cholesterol to coronary artery disease as follows:

1. Some inborn or acquired diseases with hypercholesterolemia are associated with premature atherosclerosis.

2. Serum cholesterol levels are higher than usual in persons with coronary artery disease.

3. Persons with high cholesterol levels in prospective studies developed coronary heart disease more often than those with normal levels.

4. The mortality rate from coronary heart disease in different countries varies in relation to the average cholesterol values (or dietary fat intake).

5. Experimentally induced hypercholesterolemia in animals is associated with atherosclerotic deposits.

6. Atherosclerotic plaques contain lipids similar in composition to those in the blood.

There are no long-term studies to indicate that a restriction of dietary cholesterol in children would reduce the frequency of coronary heart disease, although a few such studies are being initiated.

Until further evidence is available what should the physician recommend regarding modification of present diets?

1. Children with evidence of type II hyperlipi-

demia should be placed on a low cholesterol, low triglyceride diet, and other members of the family tested.

2. Parents who request information regarding diets could be advised that no harm would occur, and some benefits might accrue, from moderate dietary alterations such as the exclusion of excessive fried foods and those high in saturated fats. For children with a strong family history of diabetes or of early coronary heart disease, such a regimen should be urged. The avoidance of obesity and smoking should be recommended for all children.

There is no evidence for manipulation of the infant diet (low fat, etc.), but parents must be convinced that an overfed baby is not necessarily the healthiest, and above all that an "adequate" diet is essential.

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Irrationalities in Health Care Delivery

It is time that some inherent irrationalities in health care delivery be recognized and that a more realistic and substantive effort be made to accommodate them in the proposals that are being made to improve health care services. These irrationalities are reflected in some inconsistent and at times mutually exclusive solutions which are being advocated by responsible authorities. For example, on the one hand the medical profession is being urged to return to something more like the traditional practice of yesteryear with the emphasis on family physicians readily available to patients wherever they are, while at the same time and sometimes by the same people it is being pressured to form closely knit groupings of specialized physicians around a hospital center as a well-defined "health maintenance organization." Or again, while the national rhetoric calls for a single level of high quality care for all, there are major efforts to encourage the training and licensing of many kinds of new professionals who will perform many similar or identical services with different degrees of training, a situation which will inevitably create multiple levels of quality. And while the general complaint is that medical care is becoming too impersonal or "dehumanized," there is a call, even a clamor, for more organization, more efficiency and more cost effectiveness which, if it can be achieved to the extent thought needed, will hardly improve either personalization or "humanization" in health care. These can be said to be not only inconsistencies but irrationalities. However, they all reflect a much more basic inconsistency.

There appears to be a very fundamental inconsistency between science which is inherently rational and efficient, and human nature and human society which theoretically tries to be rational but simply is not. Just as biochemistry in nature—and this includes the biochemistry of human beings—always seeks the most economic and efficient means to its end, so generally does all science and technology. But the decision-making behavior of human beings and their democratic societies is something quite different. It tends to be emotional, it is often irrational and all too frequently anything but efficient. This inconsistency of rational scientific and irrational human components appears to be a basic and unresolved dilemma of modern medicine and modern society, since both depend not only upon science and technology, but upon human behavior in the essential decision-making. This appears to be the root of many, if not most of the irrationalities in health care delivery.

Human decisions are and always will be major components of medical and health care. They are made by patients, physicians, committees, governments, the public and many others, and there will always be irrationalities in many of these decisions. The question of how long a patient should remain in a hospital and the attempts to rationalize this for purposes of payment point up the kind of problem. While a "scientific" decision made by a programmed computer would be rational and efficient in its own terms, it would generally fail completely to satisfy the realities of a specific human situation or the people involved.

All of this suggests that the irrationalities inherent in human behavior must be taken into more account than is the case at present if there is to be much more rationality, system or satisfaction in health care delivery. This has so far not received the attention it deserves from those who seek to improve the health care system.

—MSMW

Pancreatitis, the Gastroenterologist's (and Everyone Else's) Enigma

IN 1966, ZIMMERMAN AND JANOWITZ[1] stated: "Inflammatory pancreatic disease of all forms continues to be an ill-defined collection of puzzling entities. No perfect etiological or clinical separation has yet been obtained. Different investigators have devised various experimental methods of inducing pancreatitis. Bile reflux, biliary tract disease and alcoholism as associated findings have previously been documented and continue to be investigated." Unfortunately, circumstances remain essentially the same and little has been added in the intervening six years to change this opinion. Reflux of bile and other substances up the pancreatic duct in man has only been assumed, not proved.

Elsewhere in this issue of CALIFORNIA MEDICINE, Geokas has presented a review of recent developments in experimental and acute clinical pancreatitis. He qualifies some of his presentation with: "On the other hand, speculation and personal opinion on controversial points concerning pathophysiology, differential diagnosis, metabolic consequences and treatment will be discussed." This is appropriate since most of the conclusions regarding acute pancreatitis, particularly pathogenesis in man, are speculation and not proved; indeed pathogenesis may not be susceptible to proof.

A vast, inconclusive and confusing literature exists on experimental pancreatitis. The disease has been induced, Geokas points out, in a large number of species. Despite the brilliance of Claude Bernard's experiment, his observations may have set back research in acute pancreatitis by 114 years. Most experimental pancreatitis has resulted from injection of various substances into the pancreatic ducts or into the gland itself. A usual prerequisite for inducing pancreatitis is that the injected substance be introduced at a sufficiently high pressure to produce mechanical injury to the tissue. Some exceptions include those varieties of experimental pancreatitis resulting from various microbial toxins, venoms, infectious agents such as Coxsackie viruses, and cytotoxic substances which do not occur in the body or are administered as nonphysiological concentrations. Often, the experiments appear to be designed to support the investigators' preconceived conclusions. Unfortunately, no experimental pancreatitis is the same as the *de novo* disease occurring in man, whatever the cause.

A great number of the experimental models result in hemorrhagic, necrotic or suppurative pancreatitis. It is reasonable to speculate that these varieties occurring in man are due to "autodigestion." On the other hand, in fatal human edematous pancreatitis, little acinar necrosis, if any, is present and it is difficult to invoke autodigestion as a pathogenetic mechanism.

Approximately 80 different clinical etiological associations have been made with acute pancreatitis. It is still not certain that pancreatitis associated with these etiologic companions are the same or different diseases. The pancreas, as all highly specialized tissues, has only a limited number of ways to react to injury. It is also not known whether necrotic, hemorrhagic, or suppurative varieties represent progression from acute edematous pancreatitis.

As Geokas points out, the pathogenesis of acute pancreatitis is unknown. The zymogen granule with its membrane, the storage form of proenzymes, is seen in the resting state. With prolonged stimulation, enzyme secretion by the pancreas continues at a high level without the formation of granules.[2] This prolonged stimulation without zymogen granule production does not cause pancreatitis either in man or in experimental animals. A protective role of the zymogen membrane is difficult, if not impossible, to prove; it may be merely a structure for concentrating proenzymes.

The phenomena which have been observed—active proteolytic enzymes in ascitic and pleural fluid, phospholipase A in experimental exudates, chymotrypsin in serum in patients, decreased proelastase and active elastase in the pancreas, decreases in lecithin and increases in lysolecithin —could all be the result of pancreatitis and have little or no role in pathogenesis.

A strong argument has been advanced for a possible role of phospholipase A and lysolecithin.[3] Two percent lysolecithin, ten times physiological concentrations, produces extensive necrosis in the pancreas of rats when injected into the duct under "slight pressure." The effect of physiological concentrations is "markedly less." The sources of phospholipase A and lecithin in these experiments are also important. In studies of the gastric mucosal barrier, lysolecithin from purified egg lecithin and phospholipase A from *Naja naja,* the hooded cobra, broke the mucosal barrier. Human pancreatic juice containing phospholipase A, with or without added bile salts, had no effect or did phospholipase A procured from venom from Russell's viper.[4] Furthermore, the human small intestine contains large quantities of lysolecithin during fat digestion but mucosal damage does not result from its presence.[5] Until it can be shown that endogenous proteolytic, elastolytic, lipolytic and lysosomal enzymes are cytotoxic *in vivo,* without artificial manipulation, their role in the pathogenesis of pancreatitis must remain speculative. If these enzymes are crucial in pathogenesis, their activity must follow the insult to the gland.

The treatment of pancreatitis is empiric. Because of the observation of elevated serum and urinary amylases following administration of narcotics, some physicians have been reluctant to provide adequate analgesia for the pain of pancreatitis. Stimulation of pancreatic secretion in patients with acute pancreatitis with secretin and cholinergic agents after the administration of morphine, does not result in deterioration of their clinical condition, although serum amylase rises.[6] Analgesia should be selected for efficacy of pain relief. While pentazocine produces a statistically lower rise in bile duct pressure than morphine,[7] a biological significance of this observation is not established. Furthermore, these rises were in the order of 8.5 cm of bile, less than 1.0 mm of mercury—a modest rise at best.

Acute pancreatitis remains a serious disease. Mortality in hemorrhagic, suppurative or necrotic pancreatitis ranges from 50 to 90 percent. Acute edematous pancreatitis has a mortality in the order of 5 percent. Controlled data establishing a superiority of either aggressive medical or aggressive surgical therapy of severe pancreatitis are not available. These data are mandatory before surgical operation can be advocated as routine in acute pancreatitis. Although most patients with acute edematous pancreatitis recover with the measures described by Geokas, these patients should be seen early by a surgical consultant in anticipation that one of the serious complications might develop.

In the presence of pancreatic abscess, it is unlikely that antibiotics will attain bacteriocidal levels in this poorly perfused tissue. Combined surgical and appropriate antimicrobial treatment are required for this dire complication.

Although theoretically sound, the routine administration of antibiotics to prevent secondary infection should not be generally adopted until there is controlled data establishing efficacy. Indiscriminate administration of antibiotics carries the risk of developing resistant strains of bacteria such as resistant staphylococci and the many species of resistant Gram-negative bacteria, which could lead to serious medical problems.

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Maternal Death Due to Uterine Hemorrhage

THE MATERNAL MORTALITY RATE in California continues to fall. In the past four years the decline has been due largely to a decrease in deaths related to illegal abortion. A small but significant number of deaths from uterine hemorrhage continues despite increased availability of blood, fibrinogen and plasma expanders. Moreover, blood loss may contribute to maternal deaths due primarily to sepsis, another significant cause of maternal mortality. We feel that each pregnancy should represent a voluntary act on the part of a woman who then accepts certain physical risks in bearing a wanted child. Obviously, strenuous efforts must be made to minimize all preventable causes of maternal death and disability.

Elsewhere in these pages, Hammond dramatically documents the persistent problem of massive obstetric hemorrhage. He identifies the patient at high risk as a multipara over the age of 30, and the significant preventable factor as inadequate blood or fibrinogen replacement too late in the course of bleeding. It is clear that several important therapeutic measures must be taken to minimize the risk of sudden massive blood loss from the gravid or puerperal uterus.

The safe administration of blood requires a complete crossmatch which in itself takes approximately two hours. This inevitable delay means that the need for blood must be anticipated. Blood must be ordered before the onset of significant hemorrhage. Foresighted obstetricians order blood for every patient at high risk when she is admitted to the labor suite. In addition a slow intravenous infusion through a large-bore needle or plastic cannula is begun before an emergency situation develops. Attempting to place an intravenous needle in a collapsed vessel is tedious and time consuming. While compatible blood is being prepared the patient's circulation can be maintained for a time by rapid intravascular infusion of isotonic solutions or plasma even in the presence of significant blood loss.

It is extremely important that all pregnant women have an antibody screen when first seen for prenatal care and again in the third trimester. Approximately 4 percent of women have atypical antibodies, a factor which often significantly limits the number of potentially compatible units of blood available. If these patients are identified in advance, a frustrating search for satisfactory blood replacement can be avoided. In areas where large stores of banked blood are not available, donors can be matched and be on call should an emergency arise.

The treatment of uterine atony after delivery of the placenta requires oxytocics and uterine massage. We must also realize that a uterus contracts poorly in the presence of hypotension when it is likely to be under-perfused with hypoxic blood. Uterine contractility will improve dramatically with the reversal of shock. Hammond also emphasizes the need for uterine exploration to remove placental fragments. These tissues prevent maximum uterine contraction, without which immediate puerperal hemostasis cannot occur. Intrauterine exploration may require general anesthesia. Its omission in some of Hammond's cases suggests incomplete anesthesia coverage, a situation which plagues many obstetrical units throughout the United States.

A labor suite must provide for prompt blood replacement and meticulous maternal care. An ideal obstetrical unit must also have the capacity to perform major obstetrical surgical procedures (including cesarean section, uterine artery ligation and hysterectomy) and provide intensive cardiopulmonary resuscitation of the newborn. This total anticipation implies not only the frequent use of up-to-date machines to monitor maternal and fetal physiologic changes but also the constant presence of people trained to interpret and act upon the data. Furthermore the best people and the finest tools require efficient utilization to maintain peak effectiveness. In obstetrics each maternity unit must be examined critically to determine whether it meets advanced medical standards of management 24 hours a day. Smaller units in urban areas will have to be consolidated, while strategically placed centers in rural areas will require reinforcement and an efficient transport program for high risk patients. Considerable soul searching and objective analysis is required of interested physicians and hospital administrators to make these changes promptly and equitably. These necessary new arrangements are required for the maximum protection of the upcoming generations.

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Three Political Philosophies And Medical Care

IT HAS RECENTLY BECOME obvious that today there are three major political philosophies in America. While they overlap to some extent, they may be crudely separated out as conservative, liberal and what might be called protest.

Each has its contribution to make to the melting pot of American political thought and each its contribution to the philosophy of medical and health care. Each has its advocates among physicians. And, as is usually the case with conflicting ideologies, there is something of value in each of them.

The conservative tradition in medicine is strong. It holds that there is always a reason for things being the way they are and they are probably best left the way they are unless there is clear evidence that change will bring improvement. In a sense this is an expression of the "do no harm" caveat in medicine. The conservative tradition also holds that health and health care are pretty much an individual responsibility as long as the individual is capable of exercising this responsibility. It also supports the principle of free enterprise in medical care with all that this implies.

The liberal tradition in medicine is also strong and deeply rooted. It holds that the benefits of medical and health care, like many other things, should be equally available to all, and that there is a responsibility for physicians to help bring this about through both personal and social action. This may be viewed as the positive counterpart of the long-standing position of the medical profession that no one should be without care who needs it. But liberalism in health care now goes further than this and undertakes to spread health care around in aggressive and occasionally forcible fashion by planning, programming and sometimes legislating the kind of health care that is thought best for those who are to receive it. All that this entails is becoming evident in the current experience with government programs and social action by others in the field of health care.

The new protest movement, hardly yet a tradition, appears to hold that the established order of things, with all of its free enterprise, planning, programs and legislation, has become much too cumbersome, rigid and unresponsive to human needs and now must undergo radical change. It is not yet clear just what the changes are to be or just what is to replace the established order that will be more responsive, but the thrust is there and it seems to be powerful. Already in health care we are beginning to see medical services being rendered outside of the traditional establishment environment in "free clinics" and other situations which are more in keeping with the culture, life-styles, habits and self-determined needs of those who are to be served than is the traditional doctor's office or hospital clinic. And lest it be forgotten, there is precedent in America for a successful protest against an unresponsive establishment. In the 18th century when the establishment proved too intransigent it was displaced by a new order of things. The medical establishment today is on test as we well know.

Each of these three political philosophies has contributed and will contribute more not only to the evolution of American political thought, but to the evolution of health care as well. Each philosophy is in obvious conflict with the others, but each has a point or two which should and must be preserved, strengthened and built into medical and health care as they evolve, we hope flexibly and responsively, in this nation. As far as medicine and the medical establishment are concerned, the energy and emphasis should be more upon realizing the positive values in each of these philosophies and less upon debating and battling over their inherent conflicts.

—MSMW

THE AGE INCIDENCE OF ACCIDENTS

Despite prevailing impressions to the contrary, there has never been sufficient evidence to warrant a conclusion that aged individuals who have no apparent disability or disease account for more than their share of accidents. Actually there are now enough studies available to show that the older worker, particularly the skilled worker, has in fact a smaller incidence of injury than a younger, inexperienced man. With respect to incidence of injury, sound judgment seems to be a more important factor than fast reaction times.

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CASE REPORTS

Refer to: Stauffer JL, Goldman MJ: Bacterial endocarditis due to Actinobacillus actinomycetemcomitans in a patient with a prosthetic aortic valve. Calif Med 117:59-63, Aug 1972

Bacterial Endocarditis Due to Actinobacillus Actinomycetemcomitans In a Patient with a Prosthetic Aortic Valve

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A 42-YEAR-OLD MAN WHO HAD had a Starr-Edwards prosthetic aortic valve inserted five years previously was admitted for evaluation of fever, chills, nocturnal diaphoresis, and weight loss. Splenomegaly, anemia and microscopic hematuria were found on admission and a diagnosis of bacterial endocarditis was made. Seven of nine initial blood cultures yielded Actinobacillus actinomycetemcomitans. The patient was treated with penicillin and streptomycin over a six-week period, cure apparently resulting. This represents the first report of Actinobacillus actinomycetemcomitans endocarditis in a patient with a prosthetic heart valve. The clinical experience of infection due to Actinobacillus actinomycetemcomitans is reviewed.

Actinobacillus actinomycetemcomitans (A.a.) is a rare cause of bacterial endocarditis. Twenty-three cases of A.a. endocarditis are cited by Page and King in an extensive review of human infection due to this organism and Hemophilus aphrophilus.[1] However, only eight cases of endocarditis in which A.a. was the sole infecting microorganism have been previously described in detail.[2-9] Five of these eight patients had underlying rheumatic valvular heart disease; one had a bicuspid aortic valve and coarctation of the aorta, and one had no underlying heart disease. In one case, sufficient information to determine the presence or absence of previous heart disease was lacking. Actinobacillus actinomycetemcomitans endocarditis has not been previously described as a complication of a prosthetic valve operation.

Case Report

The patient, a 42-year-old white man, had rheumatic fever at age 21 with subsequent aortic insufficiency, complicated by congestive heart failure, chest pain and dizziness. He was said to have had mycardial infarction at age 28. He was admitted to the San Francisco Veterans Administration Hospital for the first time on May 31, 1961, with a history of fever to 104° F, chills, diaphoresis, and anorexia for the preceding ten days. No physical findings of bacterial endocarditis were present and five blood cultures, urine cultures and throat culture were negative. It was felt that he had a viral illness, and he improved without specific treatment.

On May 15, 1962, and again on May 27, 1965, he underwent right and transeptal left heart catheterization which confirmed the presence of moderately severe aortic insufficiency. On February 22, 1966, he was readmitted because of progressive angina and dyspnea on exertion. Early in the hospital course, he had a non-specific febrile illness attributed to "flu," and all of 20 blood cultures were negative. He improved without specific therapy. On March 9, 1966, a Starr-Edwards prosthetic aortic valve was inserted. At operation the aortic valve cusps were found to be thin and delicate without fibrosis, but because of redundancy they failed to coapt and thus produced aortic insufficiency. It was

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felt that the valve defect was due to rheumatic valvulitis. The postoperative course was complicated by intermittent fever, lymphocytosis and splenomegaly, which were attributed to postperfusion syndrome. No embolic manifestations or changing murmurs were present to suggest bacterial endocarditis and 48 out of 50 blood cultures were negative. The other two yielded an anaerobic diphtheroid and Pseudomonas, both presumably contaminants. The patient was treated with corticosteroids, with gradual improvement. When discharged on May 28, 1966, the patient had a grade II/VI diastolic murmur along the left sternal border. Hemoglobin was 12.1 grams per 100 ml of blood and the hematocrit was 36 percent.

Subsequently the patient did well until April 1969, when he had an episode of infectious hepatitis. During that admission, a new grade III/VI pansystolic ejection murmur was heard over the entire precordium. The diastolic murmur was unchanged; the spleen was not palpable, and no other signs of bacterial endocarditis were present. One blood culture was negative.

The patient was readmitted on December 21, 1970, at the age of 42. Seven weeks previously he had been struck on the leg by a falling desk, which caused a skin abrasion. The next day he began to experience chills, fever, nocturnal diaphoresis, anorexia, weakness and malaise, and over the next week he lost 14 pounds. On November 19, 1970, he consulted a private physician, and physical examination was unrevealing except for aortic systolic and diastolic murmurs described above. A complete blood count and urinalysis were normal. The sedimentation rate was 75 mm in one hour. Two blood cultures were negative. Erythromycin was given, 250 mg orally four times a day for five days, with considerable symptomatic relief. Two weeks later he again experienced malaise and fever and was treated with erythromycin by mouth for ten days, with improvement. No further blood cultures were obtained. However, nocturnal diaphoresis and fever to 38.9 C (102° F) recurred and on December 16, 1970, the tip of the spleen was felt. He was then referred to the San Francisco Veterans Administration Hospital. The patient denied recent dental or urological manipulations and had had no known recent urinary or respiratory infections.

On physical examination he appeared acutely ill. Blood pressure was 115/70 mm of mercury, pulse 90, temperature 37.1° C (98.8° F). The skin was pale; no splinter hemorrhages, Osler's nodes, Janeway lesions, or mucosal lesions were present. No Roth spots were seen in the fundi. The lungs were clear. A grade III/VI harsh systolic ejection murmur was heard over the aortic area radiating to the neck, and a grade II/VI diastolic descrescendo murmur was heard along the left sternal border; both murmurs were unchanged from April 1969. The prosthetic valve sounds were judged to be within normal limits. The liver was felt 3 cm below the right costal margin. The spleen tip was felt and tenderness on pressure was noted. Neurological examination was unremarkable except for mild generalized weakness.

Admission laboratory data included hemoglobin of 12.3 grams per 100 ml of blood, hematocrit of 39 percent and leukocytes 9,400 per cu mm with 79 percent neutrophiles, 17 percent lymphocytes, 3 percent monocytes, and 1 percent band forms. The corrected Wintrobe erythrocyte sedimentation rate was 30 mm in one hour (normal 0-10 mm). The platelet count was 220,000. Urinalysis showed 100 to 200 red blood cells per high power field. Blood urea nitrogen, creatinine, fasting blood glucose, total protein, albumin, alkaline phosphatase, SGOT, uric acid, and electrolytes were within normal limits. A cardiac x-ray series showed clear lung fields, normal heart size and prominence of the aortic arch; the prosthetic valve was in appropriate position. An abdominal x-ray confirmed the presence of slight splenomegaly. Electrocardiogram showed left ventricular hypertrophy, with no significant change since September 17, 1968. No evidence of aortic ball variance was seen on a phonocardiogram.

The admitting diagnosis was bacterial endocarditis. Nine blood cultures were obtained in the two-day period before the initiation of antibiotics. On the second hospital day the patient had fever of 38.8 C (101.9° F). Therapy with penicillin G, five million units intravenously every six hours, and streptomycin, 500 mg intramuscularly every 12 hours, was begun. On this regimen he became afebrile by the eleventh day. Streptomycin was discontinued after 19 days because of signs of eighth nerve toxicity, which subsequently disappeared. After three weeks of antibiotic therapy, serum was bacteriostatic and bactericidal against the organism described below at a dilution of 1:8 immediately after penicillin administration and at a dilution of 1:1 one hour and 45 minutes afterward. The penicillin dose was therefore increased to 30 million units per day (five million units intravenously every four hours) and probenecid was added. On this regimen, which was maintained for an additional three weeks, serum was bacteriostatic and bactericidal at a dilution of 1:128 immediately after and at a dilution of 1:16 one hour and 15 minutes after penicillin administration. During the six weeks of penicillin therapy the microscopic hematuria and splenomegaly gradually cleared. There was no change in the heart murmurs heard on admission. The patient remained afebrile except for transient fever during the fifth week of therapy, which was attributed to a "flu" syndrome.

The first of the nine blood cultures yielded two strains of diphtheroids, thought to represent contaminants. Of the remaining eight, one was negative and seven grew, after five days of incubation, a fastidious, Gram-negative coccobacillary organism which was later identified by the National Center for Disease Control in Atlanta, Georgia, as Actinobacillus actinomycetemcomitans (N.C.D.C. number 51-B7359-71). The biological and biochemical properties of this organism, which allowed for its initial recognition at the N.C.D.C. are shown in Table 1. Antibiotic sensitivities, as determined by the disc method, were difficult to determine and inconsistent because of the low yield of organisms. Eight blood cultures were obtained over a five and a half week period after the initiation of antibiotics. All were negative. After conclusion of antibiotic therapy the patient was observed for four days and in that time had no fever or other evidence of recurrence of illness. On February 8, 1971, he was discharged to the care of his private physician. Results of cardiac examination showed no change, the spleen was not palpable, and there was no hematuria. He was doing well on follow-up outpatient visits at three weeks and again at four months after discharge.

TABLE 1.—*Biological and Biochemical Properties of Actinobacillus Actinomycetemcomitans Isolated in Case Here Reported**

1. Fermentation Characteristics

Medium	*Result*
glucose	+(A)†
mannitol	+(A)
maltose	+(A)
xylose	−
lactose	−
sucrose	−

†(A) = acid production

2. Growth on Selected Media

Medium	*Result*
MacConkey	−
S.S. plate	−
Citrate slant	−
Urea	−
Nitrate broth	+
Indol broth	−
Gelatin stab	−
H_2S paper	1+

3. Miscellaneous Characteristics

CO_2 required for growth
37° C temperature required for growth
Catalase production positive
Oxidase production negative
Motility absent

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*We acknowledge the assistance of Robert E. Weaver, M.D., of the Special Bacteriology Laboratory, Clinical Bacteriology Unit, National Center for Disease Control, Atlanta, Georgia, in identification of this organism.

Discussion

Actinobacillus actinomycetemcomitans is a bacterial species first described in 1912 by Klinger, who isolated it from the pus of patients with actinomycosis.[10] Numerous subsequent reports describe the close association between this organism and Actinomyces.[11-14] In 1951, Thjøtta and Syndes reported a case of infection of the jaw of a young woman after tooth extraction, but the fermentation characteristics of the organism isolated were not those of A.a.[15] In 1953, Vallee and Gaillard mentioned (in a footnote) isolation of A.a. in blood cultures of patients with endocarditis, but no details were given.[16] Because the organism they described fermented arabinose, it is doubtful that it was in fact A.a. King and Tatum were the first to describe unequivocal cases in which A.a. was the sole infecting agent in man.[17] They reported 32 cases of documented A.a. infection unassociated with actinomycosis and compared the biochemical and serological characteristics of 33 strains of A.a. and 34 strains of Hemophilus aphrophilus, an organism closely related to A.a. These data have more recently been reviewed by Page and King, who noted that of the 32 cases in which A.a. was isolated, 23 were cases of endocarditis, which seems to be the most common type of infection due to this organism.[1]

Rarely, however, is A.a. isolated as a pathogen

TABLE 2.—*Data on Reported Cases of Actinobacillus Actinomycetemcomitans Endocarditis*

Source	*Age*	*Sex*	*Heart Disease*	*Cultures Positive*	*Antibiotic Treatment*	*Outcome*
1. Thomas[2]	49	M	Bicuspid aortic valve and coarctation of aorta	4/?	Penicillin, streptomycin, erythromycin, chloramphenicol	Died
2. Serra and Tonato[3]	41	M	Rheumatic	12/12	Ampicillin, streptomycin	Cured
3. Vogelzang[4]	27	M	Rheumatic aortic stenosis	Initial cultures negative; all positive at 8 days	Penicillin, tetracycline, streptomycin	Died
4. Goss, et al[5]	39	M	No underlying disease	10/?	Penicillin, streptomycin	Died
5. Overholt[6]	57	M	Rheumatic mitral insufficiency	6/6	Penicillin, chloramphenicol, streptomycin	Died
6. Kayser[7]	52	M	Rheumatic mitral valvulitis	4/?	Cephalothin, penicillin, streptomycin	Cured
7. Underhill[8]	68	M	Mitral valve disease (? rheumatic)	More than 9 cultures positive	Ampicillin, streptomycin	Cured
8. Mitchell and Gillespie[9]	50	M	Rheumatic	Four initial cultures negative; three subsequent cultures positive	Penicillin, streptomycin	Cured
9. Present Case	42	M	Prosthetic aortic valve	7/9	Penicillin, streptomycin	Cured

in human infection, possibly due to its fastidious growth characteristics and difficulty in identification. These factors presumably account for failure of two blood cultures obtained in the first week of our patient's illness to yield A.a. Page and King reported seven patients with soft-tissue lesions from which A.a. was recovered, and in four of them the clinical diagnosis was actinomycosis. Of the remaining three, one had an abscess of the jaw and another had a facial abscess. A.a. has also been recovered as a pathogen in at least one case of urinary tract infection.[18] A.a. has been found in the normal flora of the mouth.[19-20] A.a. endarteritis has been described in a patient with a congenital fistula of the right coronary artery to the right ventricle.[21]

Numerous articles reviewing experience with endocarditis make no mention of A.a.[22-27] Only eight cases of well-documented A.a. endocarditis have been found in the literature; four were fatal (Table 2.) It is of interest that the patient described by Vogelzang and our patient were from the same county (Stanislaus) in California. Five of the nine patients had illnesses of varying types for which they were treated with antibiotics, usually penicillin, shortly before the onset of clinically recognizable endocarditis.

The portal of entry of the organism in our case is not clear. Entry through the skin abrasion acquired seven weeks before admission is speculative. In the case reported by Underhill, it was presumed that a dental abscess was the portal of entry, and the patient of Mitchell and Gillespie had a dental extraction covered with penicillin six months before the onset of symptoms. In view of the findings of A.a. in the normal mouth flora, these reported cases suggest that oral lesions may be a significant mode of entry. Major embolic complications, common in previous cases, were absent in our patient. In each of the fatal cases cited, autopsy confirmed endocarditis involving an abnormal heart valve.

Postcardiotomy endocarditis is most often caused by Staphylococci,[28-29] but a wide variety of other microorganisms have been implicated. The bacterial group is diverse and includes Streptococcus, Escherichia coli, diphtheroids, Alcaligenes faecalis, Pseudomonas, Achromobacter species, Aerobacter, Proteus, Paracolobactrum aerogenes, Herrellea, Paracolon hafnia, Serratia marcescens, and Neisseria perflava.[28-32] The fungal group includes several species of both Candida and Aspergillus.[29,33,34,35] Although postcardiotomy endocarditis usually appears within the first two to four weeks after operation,[28] cases have been reported as long as six years after a surgical procedure.[36-37] In our case, 56 months elapsed between operation and onset of symptoms of endocarditis. The occurrence of prosthetic valve endocarditis long after operation raises questions about the origin of the infection.[32] Sources such as tooth extractions, urinary tract manipulations, respiratory infections, pyelonephritis, and pyoderma have been cited.

Prosthetic valve endocarditis is associated with high morbidity and mortality.[38] In 97 cases recently reviewed by Shafer and Hall, the mortality rate was 72 percent.[32] Nevertheless, cure of prosthetic valve endocarditis has been accomplished with antibiotic therapy alone or in conjunction with surgical operation. Conservative management with antibiotics alone has generally been unsuccessful, although in three of ten cases cited by Killen the patient survived without resort to surgical operation.[39] There is uniform agreement that replacement of the infected prosthetic device is indicated for infections unresponsive to antibiotics alone and for hemodynamic imbalance due to valvular insufficiency or obstruction by vegetations or thrombi. The case herein described represents another report of apparent cure by antibiotic therapy. The high mortality of prosthetic valve endocarditis emphasizes the need for early recognition of this complication and treatment with appropriate antibiotic therapy.

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Severe Obstructive Nephropathy

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URINARY TRACT OBSTRUCTION has a profound effect on renal physiology and may be indistinguishable from severe primary renal disease. The standard textbooks[1,2,3] provide excellent reviews of historic and current physiologic thinking, yet beyond these there are few quantitative reports of high grade obstructive nephropathy.

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The severe case here reported, in which there was striking recovery of renal function following the relief of obstruction, is an example of the importance of constant suspicion of obstructive disease in patients with deteriorating or terminal renal function, particularly of recent onset and rapid or intermittent course.

Report of a Case

The patient was a 52-year-old man seen for the first time at San Joaquin General Hospital with a two-week history of progressive malaise, weakness and poor appetite. He denied nausea, emesis, back pain, stool changes, paresthesias, arthralgia, rash, hematuria and venereal disease. He had occasionally taken anti-hypertensive medication since 1948 and had had infrequent dysuria for the same length of time. He denied urinary frequency or nocturia, hesitancy, incomplete emptying or multiple voiding, urgency or split stream.

On physical examination he was observed to be lean, oriented but obtunded, and to have pale conjunctivae and uremic frost about the face. Respirations were 10 per minute and deep. The blood pressure was 180/110 mm of mercury, the pulse 90 and regular, and the temperature normal. The fundi revealed Grade II atherosclerotic changes. Inspiratory rales were present at both lung bases. On palpation the urinary bladder appeared not to be enlarged. The prostate was tender, with three-plus enlargement bilaterally. Muscle fasciculation was noted, and the deep tendon reflexes were very hyperactive.

Laboratory Examinations

Blood urea nitrogen was 240 mg and creatinine 23.4 mg per 100 ml, potassium 6.3 mEq and plasma bicarbonate 5 mEq per liter, pCO_2 15 mm of mercury and arterial pH 7.06. The SGOT was 34 units, alkaline phosphatase 14 KA units, and uric acid 6.5 mg per 100 ml. Total protein was 8.4 grams per 100 ml with albumin of 3.5 gm. Cholesterol content was 105 mg, calcium 10.9 mg and phosphate greater than 10 mg per 100 ml.

Specific gravity of the urine was 1.008 with 0 to 2 red and white blood cells per high power field. The electrocardiogram reflected left ventricular hypertrophy, clockwise rotation, and nonspecific ST-T wave changes. A chest roentgenogram showed right lower and left upper lobe parenchymal infiltration.

Hospital Course

When an indwelling Foley catheter was placed, 1,800 ml of sterile urine flowed out immediately, and the output then varied from 1,700 to 3,500 ml per day during the rest of the hospital stay. Peritoneal dialysis was instituted and continued for 36 exchanges in as many hours. Serum creatinine was 2.1 mg per 100 ml at the termination of dialysis. Creatinine clearance the next day with a Foley catheter in place was 46 ml per minute, and the protein content of a 24-hour urine specimen was 1.9 grams. Serum potassium was 3.8 mEq per liter, pCO_2 30 mm of mercury and arterial pH 7.35. By the sixth hospital day, the patient ate and ambulated well and his blood pressure was 115/70 mm of mercury. All electrolytes and the pH were stable, and the proteinuria had cleared. On the tenth day, he was dismissed with an indwelling Foley catheter.

Subsequent routine intravenous pyleography revealed decreased function on the left side, but no obstruction above the level of the prostate, and a urinary bladder diverticulum was demonstrated at cystoscopy. Two weeks after transurethral resection, blood urea nitrogen was 21 mg and the serum creatinine 0.89 mg per 100 ml, with a creatinine clearance of 140 ml per minute. Microscopic examination of a prostatic specimen was compatible with benign prostatic hypertrophy and chronic prostatitis.

Discussion

That the kidney continues to function even during complete obstruction has been well documented in standard texts. If it were not so, then primary atrophy would occur instead of dilatation, and the prompt diuresis obtained after relief of the obstruction could not take place.

This patient may well have had chronic renal disease in the form of nephrosclerosis, compatible with the diagnosis of long-standing hypertension. However, a significant degree of sclerosis seems unlikely because of the minimal retinopathy and the return of blood pressure to normal upon relief of obstruction. The history was compatible with chronic prostatitis, and presumably benign prostatic hypertrophy, while acute prostatitis accounted for the relatively acute episode of obstruction.

Although it is likely that the spontaneous diuresis following relief of the prostatic obstruction would have brought about return of blood chemical factors to normal, peritoneal dialysis was instituted because of the pronounced uremia. Return of normal function as measured by common laboratory chemical determinations followed definitive therapy. The patient showed no evidence of the polyuria frequently observed in such cases,[4,5] or of sodium and potassium wasting[6] or the more rarely reported nephritides following relief of the obstruction. We have no evidence that maintenance on peritoneal dialysis during the immediate post-obstructive period influenced development of these states.

Diagnostic x-ray evaluation was easily accomplished with a routine (50 ml contrast medium) intravenous pyelogram after the obstruction was relieved. This again demonstrated basically good renal function. If excellent recovery had not been achieved, the radiologic information—that is, kidney size, evidence of obstruction, and calyceal configuration—could have been obtained with high-dose (150 ml contrast medium) pyelograms with nephrotomograms; and had that procedure failed, the high-dose pyelogram would then have been repeated after dialysis. This has been shown to increase the frequency of visualization in these difficult cases.[7,8] If all these procedures failed, then and only then would a retrograde pyelogram with its higher incidence of morbidity be indicated.

Obstruction to urine flow has striking effects upon renal function, yet in most cases it need not result in death. This is true especially if the obstruction is low-grade or intermittent. Because it is a common and remediable condition,[9,10] it should be kept in mind as a possible etiologic factor in patients with symptoms of terminal uremia.

Summary

Bilateral urinary tract obstruction of any cause can mimic terminal renal failure. A case is presented of a severe degree of renal dysfunction caused by prostatic obstruction to renal outflow. Renal function as measured by common laboratory means returned to normal after relief of the obstruction.

Obstructive nephropathy is more common than may be generally realized. It should be borne in mind in differential diagnosis of patients with symptoms of renal failure.

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LETTERS *to the Editor*

A Comment on Peer Review

To the Editor: In the May 1972 issue of CALIFORNIA MEDICINE, the editor aptly brings to the attention of his readers the decision of a Philadelphia court which recently ordered a physician to pay the hospital bill of a patient deemed by the judge to have been hospitalized unnecessarily. In the editorial he explores the difficulty and offers as part of his solution "peer review of what actually takes place and continuing education of all concerned" and gives this charge to the California Medical Association.

The physician today finds himself caught between the patients' desires and the limited supply (actual or economic) of available medical care. As a result of this evolvement we see increasing expectations of so-called "peer review" as the solution to the problem.

Unfortunately peer review is only one part of the equation. Efficient and high quality medical care is dependent not only upon peer review but upon other factors as well. Good medical care depends upon the sum of patient cooperation and motivation, physician skill and, when necessary, an available hospital setting. Without all these ingredients good care cannot emerge.

The editor wisely indicates that "it would appear that the best and most economical medical care rests upon the good judgment of those involved at the time and place the care is given." But he then goes on to say that "if improvements are to be made the emphasis should be upon improving judgment, and not upon punishment or professional liability or close governmental regulation of individual circumstances which by their nature defy standardization."

I would agree that improving judgment is important but the judgment that needs improving is that of the patients. By this I mean the patients' judgment which is influenced by his motivation.

As a result of outside interference his judgment/motivation has been distorted and impaired.

The editor ignores this important ingredient of good health care. All the peer review in the world of the physician is not going to motivate the patient to leave a hospital as soon as medically indicated. The crux of the matter is the almost full coverage granted the patient under such a system as Medicare which essentially removes responsibility on the part of the patient to restrain his demand. As a result a disequilibrium has been caused in the medical care equation. Over-utilization occurs and government intervention proceeds under the pretext of holding down medical costs.

When individuals must pay for their choices, even in part, they weigh the cost and restrain demand to what they feel they truly need. Individuals can voluntarily apply the brakes to both increased demands and costs. This is the market system of voluntary exchange between buyers and sellers.

Medicine is not an exact science. For example, how can one deny that an epigastric pain may not be due to peptic ulcer without doing an upper gastrointestinal series? How easy it is for the patient or even the doctor to connive at the prolongation of the patients' hospitalization to determine the presence or absence of organic disease to explain symptoms.

To symbolize the doctor's dilemma to which I refer, I cite two letters which I received within the same week. The first was a communication from the attorney of a deceased patient in which a veiled threat of legal action was made unless the hospital's utilization committee consider a reversal of their decision to terminate his client's coverage of her last week's hospitalization since this was, on the face of it, "obviously necessary" because the patient expired at home several days following her discharge.

Later that same week I received a letter from the hospital utilization committee concerning another patient. In this instance the utilization committee indicated agreement with the insurance carrier which had retroactively, seven months after the fact, denied six out of a twelve day hospitalization. The patient was being asked to pay for the balance of the uncovered hospitalization.

In both instances the patient and his family, and practically everyone else, will believe the physician to be at fault.

In Medicare and presently proposed governmental schemes we are creating a system which brings out the evil in men, and which will lead to diminished quality of, and increased cost of medical care as contrasted with the free market system. We are creating a situation wherein the patient is tempted to cheat on his illness by demanding further hospitalization. The physician is also tempted to cheat: First, by accommodating the patient to avoid his wrath and possible dismissal—as well as to diminish the threat of a malpractice suit. Second, by obtaining the further fees generated by the patient's prolonged hospitalization.

To this now is added a new potential threat to the physician, *viz.*, the "peer review" structure (utilization committee) which by its very nature will add still another hazard to the physician. By its operation it will act in such a manner as to hold the physician liable for the cause of the "unnecessary" prolonged hospitalization of his patient.

How ridiculous can all this get? How will all this affect the judgment of the physician and the care rendered the patient?

More peer review is not the answer in a profession that is being peer reviewed to death (as compared to the legal profession, for example, that does not know the meaning of the words).

The editor speaks of "improving education" of physicians by continuing education. This situation already exists. Educational opportunities for physicians abound and are widely attended. The enhancement of each individual physician's skills is insured by his ability to voluntarily pursue his own educational needs. Further coercive measures are not the answer.

In summary, therefore, to return to the editor's statement concerning the "good judgment of those involved at the time and place the care is given," the good judgment of the patient rests upon: (1) his ability to freely choose his own physician, and (2) the patient's ability to accept his part of the responsibility of his own care and thus be properly motivated. The good judgment of the physician depends on his ability to care for the patient unencumbered by outside interference which compromises his judgment as to what is best for the patient. In such a setting all are motivated to do what is right.

RAFAEL A. SOLARI, M.D.
San Francisco

On Healing the HCDS

To the Editor: Our forum, CALIFORNIA MEDICINE, has been increasingly interested in the Health Care Delivery System—Past, Present, and Future and has been giving over considerable space to musings about that system. I beg your indulgence to point out a fallacy that seems to underlie most of the pieces printed. We physicians do *not* have universal expertise in all matters related to health. In fact our area of competence is restricted to one small field somewhat related to ill-health, namely, disease. We are quite fortunate when the cause of someone's not-feeling-well is a disease; and trebly fortunate when it is one that our techniques and science can do something about; and still more fortunate yet when the afflicted actually feels himself restored to health as a result of the palliation or cure that we effect.

Were we the healers we should be (or would like to be), then might we rightly take unto ourselves the preeminent role in changing the Health Care Delivery System. (Maybe, were we real healers, there would be no need to change the HCDS.) Other people concerned with health matters know we are no more than disease technicians. When will we acknowledge it?

ALAN D. MATZGER, M.D.
San Francisco

Refer to: Harer WB Jr: Tel-Med—A public medical information service by phone. Calif Med 117:68-70, Aug 1972

In the Forefront

TEL-MED
A Public Medical Information Service by Phone

Call a Number, Ask about a Disease, Listen to a Taped Reply Provided by the County Medical Society

W. Benson Harer, Jr., m.d., *San Bernardino*

Authoritative information on a wide range of diseases—including many on which misinformation can be disastrous—is available to anyone in the San Bernardino-Riverside area who will place a phone call to an advertised number and listen to tape recordings in English or Spanish on the subjects requested.

The San Bernardino County Medical Society has made the tapes and provided an operator who plays the recordings asked for by the caller, who remains anonymous. Use of the service began instantly upon announcement of it and publication of the telephone number. There are more than 150 inquiries a day.

A library of taped messages 3 to 6 minutes long is maintained at the San Bernardino County Medical Society offices. Tapes cover a wide range of subjects from birth control to venereal disease. People desiring information dial the toll-free phone number. An operator is on duty from 9 A.M. to 8 P.M. weekdays and 10 A.M. to 6 P.M. on Saturday. He handles ten phone lines on a rotary system with tape playback devices for each line. The caller can request a tape by index number, title or subject classification. The operator plugs in the tape which then plays over the phone to the caller and automatically disconnects at the end of the message. More than 400,000 people have access to this system by a toll-free phone call. This is the tel-med project.

The public response is one of unqualified enthusiasm and support. The worried young woman can learn the signs and symptoms of pregnancy and, if needed, learn about therapeutic abortion and how to get one. The frightened teenager can learn about venereal disease and how to get free diagnosis and treatment. Concerned parents can obtain the facts about drug abuse and further advice on dealing with their teenagers. The elderly concerned about failing hearing and vision, the bride worried about feminine hygiene, the woman afraid of cancer, the man fearful of high blood pressure and heart disease—in short all classes of the population old enough and intelligent enough to dial a phone can now call in to get the basic information they need to allay groundless fears, dispel mythical old wives' tales and focus on the pertinent aspects of a disease process.

Emphasis is primarily on prevention or early detection and only secondarily on treatment. Sources of further information on how to obtain diagnosis and treatment are provided when pertinent. Moreover, the information bears the approval of their own county medical society. The public relations value to physicians is immeasurable.

In an age when physicians and organized medicine often find themselves forced into a defensive posture by wild charges of failing to meet

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The author is Secretary-Treasurer of the San Bernardino County Medical Society, and Medical Director of Tel-Med.

Reprint requests to Carla Franklin, San Bernardino County Medical Society, 666 Fairway Drive, San Bernardino, Ca. 92408.

the public needs, the TEL-MED project emerges as a bold, innovative outreach to the public —a concrete positive demonstration of the physicians' effort through the medical society to provide, free of charge, the information to help maintain health, recognize early signs of significant illness and to get help. For those with chronic illness such as diabetes and heart disease it provides information for the individual and his family on how to adjust to the illness.

In addition to the public relations value, the project has other benefits for the physician and other health care providers. TEL-MED guides the public to proper utilization of available facilities. The taped messages readily supplement physician and staff counselling for patients and their families. In short, TEL-MED has forged a new link of communication between physicians and the public to the benefit of both.

History

The TEL-MED concept was the brain child of the project director, Mr. Raymond Saar, a former aerospace engineer. He recognized the validity of the telephone information retrieval system as an effective and economical means of disseminating information. The applicability to health information was readily accepted.

Mr. Saar effectively presented his concept and the project was funded for a one-year pilot program starting October 1971. Regional Medical Programs Area VI contributed $24,500 and California Medical Education Research Foundation (CMERF) gave $10,500. The San Bernardino County Medical Society has contributed about $11,000 to bring this to fruition. The original project hoped to develop a library of 50 tapes the first year.

As a pioneering project, no guidelines or past experience were available to aid us. A steering committee was formed, yielding a relatively small but highly dedicated and productive group which pushed the project forward.

A visit to the University of Wisconsin medical tape service by Mr. Saar provided valuable insight into the only related service known to us. The library there, however, consists of tapes geared to continuing education of physicians and nurses instead of the general public.

Myriad problems cropped up in every facet of this complex undertaking, but solutions were found and needed guidance and assistance was generously provided from a broad range of technical and cultural sources.

Through systems engineering techniques, various facets of the program were developed simultaneously. Questionnaires were sent to hundreds of health service agencies, physicians and educators to establish priorities for subjects to be covered. In addition appropriate authors and sources of information were identified.

Surveys were conducted among high school and college students and a wide range of community social and service clubs to establish the areas in which the public most desired information.

Meanwhile the necessary play-back equipment was evaluated, purchased, partly built by Mr. Saar and installed. A ten-line rotary phone system was then married to our equipment.

After the subjects were determined upon, script development began. It became apparent that special techniques are involved in bringing complex medical concepts, such as relationship of blood pressure to atherosclerosis, to a level readily comprehended by the person who reads at an 8th grade level. Scripts authored by physicians are reviewed by lay workers who partly rewrite to clarify and simplify. Scripts are then separately revised by the project director and the medical director—often with much communication back and forth from all involved. The script is then ready to be recorded.

The tapes are recorded by professionals. The narrator is selected for qualities compatible with the subject—for example, a young woman for tapes on pregnancy and birth control, an older man for a tape on glaucoma. Experienced radio and TV performers have generously given their services—often offering even further refinements to the script.

The finished tape is then played to a review committee of physicians from the San Bernardino County Medical Society. This committee has final authority on placing the tape in the library for the public. About 5 percent of the tapes have been further revised or rejected at this final hurdle.

To serve fully the population of our area, the entire library is being duplicated in Spanish. The final version of the English script is translated by skilled laymen. Bilingual physicians provide the final review for the medical society and bilingual narrators record the tape.

Preliminary trials of the system were conducted in March of 1972 to validate operational readiness. When these proved successful, the first area-wide news releases went out on April 7 with a library of 35 tapes. The public response was overwhelming. The next day over 1200 calls were logged. During the ensuing 14-week period 15,995 calls were received. With the steady addition of new tapes the library approaches 100—double the first year's projected goal.

Continuous evaluation of the system is important. The number of calls to each line is logged daily. The number of requests for each tape is similarly noted. Rough estimates by the operator of age and sex of caller are compiled. During slack periods staff members also come on the line at the end of the message to interview the caller. In this manner we can check to see if the caller's needs have been met by the tape. Areas of ambiguity or insufficiency can be identified. Review and revision of scripts at least once a year is planned. More sophisticated methods of evaluating public and professional response are to be put into use.

The validity of this concept having been established in the pilot project, what of the future? The potential for this system is as vast as the need. Currently we are seeking grants to further develop and expand this program. Our project has generated great enthusiasm among other potential users such as the welfare department, county health departments, hospitals, police, probation, fire, and a broad spectrum of public service agencies who would like to provide similar services. The economy and efficiency of the TEL-MED approach cannot be matched by any other system. Such supplementary users at a modest fee could sustain the health information portion at no further cost. Special tapes for individual physicians or groups could also be developed for a nominal fee.

Currently we are applying for a three-year operational grant. This will provide for a library up to 1000 tapes. It will further establish a TEL-MED center in the Victorville-Apple Valley area to test the program in a rural area. A program such as ours also will be set up in San Diego through the San Diego County Medical Society and Area VII Regional Medical Programs to evaluate the system in a large metropolitan area. More sophisticated analysis of every aspect of the program and its impact will be conducted. With this we hope to establish a self-sustaining, ongoing program and to be able to advise other county medical societies that may wish to set up such a system.

CANCER FELLOWSHIPS

Postgraduate Fellowships in cancer for practicing physicians are available at the University of Southern California School of Medicine and the Los Angeles County-University of Southern California Medical Center. These Fellowships are sponsored by the National Cancer Institute, are of one month's duration and carry a stipend of $750. Separate programs are available in gynecological oncology, medical oncology, radiation therapy, tumor pathology and tumor surgery. Applicants should be Board eligible or Board certified and should submit a résumé of their professional background to Arthur J. Donovan, M.D., Program Director, Cancer Training Program, School of Medicine, University of Southern California, 2025 Zonal Avenue, Los Angeles, California 90033.

PUBLIC HEALTH REPORT

Frederick B. Hodges, M.D., Chief Deputy Director, State Department of Public Health

Recent Developments in Immunization

New Immunization Legislation

In March, 1972, legislation became effective requiring children in day nurseries, nursery schools, and child care centers and children entering California schools for the first time to be immunized against diphtheria, tetanus, and, for children less than seven years old, pertussis.[1] This is in addition to the requirements for poliomyelitis and measles (rubeola) immunizations which have been in effect for some years.[2,3] Provisions are made for exemption on the basis of medical contraindications or religious belief.

The major impact of the legislation will be felt with the opening of school this fall. Survey data indicate that 25 to 30 percent of those entering school for the first time will need some immunization to comply with the law. Request to physicians for the newly required immunizations will provide an opportunity to review each child's immunization status and correct deficiencies.

Immunization Needs

Immunization levels among the childhood population in California are generally high.[4] The cooperative efforts of private physicians, local public health departments, and the State Department of Public Health have achieved strong ongoing immunization programs. Special intensified efforts have been conducted in turn against poliomyelitis, measles (rubeola), and rubella as the new vaccines have become available, so that they could be given within a short period to a major proportion of the susceptible population. Despite these generally successful efforts, some substantial areas of need remain.

Measles (Rubeola)

Intensified immunization campaigns against measles were conducted throughout California during 1967 and 1968. There was a resultant marked decrease in statewide measles morbidity, with 1969 having the lowest reported measles incidence in California history: 916 cases reported or a case rate of 4.5 per 100,000 population compared with an average of 35,000 cases in pre-vaccine years.[5] Following the completion of the intensified campaigns, immunization efforts against rubeola slackened somewhat.[6] A gradual increase in rubeola morbidity followed in 1970 and 1971. The 1972 rubeola "season" showed a continuation of the increased incidence and, for the first time in three years, there was extensive rubeola epidemic activity in California. This was most dramatic in Los Angeles County, but several other counties also experienced major rubeola outbreaks.[7] While there is no reason to expect a return to pre-vaccine incidence levels, unless concerted efforts are made to assure immunization of preschool age children it can be expected that incidence will continue at an unnecessarily high level and sporadic major outbreaks will occur.

School-age children are relatively well immunized against rubeola as the result of the intensified campaigns and the immunization requirement for school admission. The major deficiencies are in the preschool age group, especially in economically disadvantaged and ethnic minority groups.[8] Cases also have occurred in children who were immunized prior to their first birthday and in some who received vaccine and gamma globulin at the same time. Continuing surveillance of vaccine efficacy emphasizes, however, that the vaccine is more than 90 percent effective. Unimmunized children have been predominantly involved in the outbreaks.[9]

Physicians are urged to immunize children as soon after their first birthday as possible and to consider re-immunizing children who may have been immunized at nine months of age or less.

Atypical measles, sometimes severe, with a variable rash, peripheral edema and pneumonia, has occasionally followed exposure to natural measles in children inoculated five to six years previously with inactivated measles virus vaccines. Untoward *local* reactions, such as induration and edema, have been observed at times when live measles virus vaccine was administered to persons who had previously received inactivated vaccine. Despite the risk of local reaction, the Public Health Service's Advisory Committee on Immunization Practices recommends that children who have previously been given only inactivated vaccine should be revaccinated with live vaccine to avoid the severe atypical form of natural measles and to provide full and lasting protection.[10]

Poliomyelitis

California continues to be free of poliomyelitis. There is evidence that immunization levels against poliomyelitis are decreasing somewhat, however, so the reintroduction of this disease is possible.[6]

The school-age and young adult population is well immunized as a result of the major campaigns of the early 1960's and the school admission requirement. The preschool age population, especially in lower socio-economic and ethnic minority groups, is less well protected.[8] Physicians are urged to do all possible to ensure adequate poliomyelitis immunization among their pediatric patients.

Rubella

More than 70 percent of the one- to twelve-year-old population in California has now been immunized against rubella.[11] Since many of the programs were conducted within recent months, morbidity figures do not yet reflect the full impact of this effort. Public programs have focused upon the pediatric population as their target with the objective of reducing potential exposure of pregnant women to the disease. A second objective, necessarily more appropriate for the individualized assessment possible in private physicians' offices, is the immunization of non-pregnant, rubella-susceptible females of child-bearing age.[12] Physicians are urged to immunize their pediatric patients and also to immunize susceptible women of child-bearing age if the necessary precautions regarding pregnancy can be assured.

Combined Vaccines

Convenience in the administration of the various live-virus vaccines has been increased by the availability of combined vaccines. Available combinations are: mumps-rubella, rubeola-rubella, and mumps-rubeola-rubella. The licensed combinations have been found to be highly effective and decrease the cost and effort of immunization to both physician and patient.[13] When patients request one vaccine, the physician may wish to consider a combined vaccine for additional protection as appropriate to the circumstances. The combined vaccines are particularly appropriate for children in the preschool age group, since large numbers of this group will have neither natural nor artificial immunity against either rubella, rubeola, or mumps.

A particular problem exists with regard to rubeola and rubella since the term "measles" has been popularly used for both of these diseases. Many parents are unsure as to which type of "measles" vaccine their child has had. It is recommended that the combined rubeola-rubella or mumps-rubeola-rubella vaccine be used for preschool children to avoid confusion.

Available Resources

Assistance for immunization activities is available from local health departments, many of which have projects funded under the Immunization Assistance Program. All local health departments receive vaccines through this statewide program. These include poliomyelitis, measles, rubella, and measles-rubella vaccines. These vaccines are also available, through the local health departments, to private physicians who agree to use them only for children through the age of

12 years at no charge for the vaccine. Project funded vaccines are also available, upon the request of the physician in charge, to neighborhood health centers and other community-oriented health facilities.

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Refer to: Lee JF: Needle Power—A report and discussion of acupuncture (Information). Calif Med 117:74-75, Aug 1972

Needle Power

A Report and Discussion of Acupuncture

JANE F. LEE, M.D., *San Francisco*

THREE-QUARTERS OF AN HOUR before the program was to begin, the seats of the auditorium of the San Francisco Medical Society started to fill. By the starting time, there was little standing room for this first demonstration of acupuncture in San Francisco. The demonstration was sponsored by the San Francisco Medical Society and the University of California, San Francisco, on May 9, 1972.

Many modern scientific theories have been advanced on the mechanisms of action of acupuncture but none are as widely accepted by acupuncturists as the ancient Chinese rationale. The Chinese believed that all things in nature are part of one essence, the "*Tchi*" (vital energy), the universal principle of the cosmos. Within the *Tchi* are contained the opposed forces of Yin and Yang. Health of body and mind is dependent upon a balance of these two principles. The time, weather, season, environment and emotions are all involved in maintaining and disturbing this balance. The doctrine of the five elements—wood, fire, earth, metal, water—is closely related to the Yin Yang principle, since the Yin Yang energy may strengthened or weakened by these five elements. The two groups of internal organs, *Tsang* (heart, liver, spleen, lungs, kidneys) and *Fu* (stomach, large intestines, small intestine, gall bladder and pericardium) are connected by 12 main channels or meridians on each side of the body through which flows the vital energy *(Tchi)*. In addition, two special channels—one front, one back—run sagitally down the midline. There are interconnecting channels between these main meridians. Along the meridians are 364 points for needle insertion.

Two physicians, Dr. Kok Yuen Leung and Dr. B. C. Pien, China-trained in traditional medicine, were invited as guest lecturers to demonstrate the needling process. Both had been trained to diagnose disease by pulse-taking and to treat by (1) administration of herbs; (2) physiotherapy—massage and exercise; (3) psychotherapy; and (4) acupuncture. Following the usual four years of medical training, these physicians continued studies in the field of acupuncture for the purpose of treatment of disease and alleviation of pain. Acupuncture in Peking today is not used only for treatment. A newer use of acupuncture is in the field of anesthesia, in which a great deal of research is being carried on. Men of science and medicine from the United States have reported on the many surgical procedures done with the use of acupuncture anesthesia.

The demonstrators at this meeting, however, were not trained in these anesthesia techniques. Their main use of acupuncture was in the relief of pain, especially in the various arthritides. They had reported success, however, in producing anesthesia to the face and jaw in treatment of tic doloreaux and toothache.

Three patients were selected for acupuncture; it proved successful in two. Pulse-taking preceded and followed the application of needles. (Pulse differences were found before and after treatment by the physicians.)

Case 1.—The patient was a 19-year-old man who was to have a prophylactic third molar extracted, and it was hoped that anesthesia could be brought about by acupuncture. Thin 2-inch fine-gauge sterilized stainless steel needles were placed along the large intestine and stomach meridian in the hand. After 15 to 20 minutes, anesthesia was produced only up the arm to the elbow and the process was abandoned.

Case 2.—The patient was a 34-year-old woman, a nurse who twice had had laminectomy and discectomy for herniated discs, a diagnosis of arachnoiditis for which a third laminectomy for neurolysis was done, and a dorsal column electric stimulator implantation in the thoracic portion of the cord to relieve bilateral leg pains.

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After the placements of needles in her legs along the gall bladder meridian and bladder meridian, the patient obtained instant relief of leg pains and on recheck two months later was still free of pain.

Case 3.—A 54-year-old male physician who had longstanding bilateral osteoarthritis of the hip and had pain down both hips and legs received the needle treatment. Definite relief of pain was felt after this procedure. The patient was admonished, however, that ten to fifteen such treatments would be necessary to obtain continuous relief of pain in this condition.

With the success in two out of three cases, the San Francisco Medical Society and the University of California, San Francisco, have opened the eyes of the Western practitioner to the possibility of adding a new kind of procedure to his armamentarium for the treatment of disease.

The University of California, San Francisco, had a follow-up session at the San Francisco General Hospital ten days later in which the Radiology Department and the Anesthesiology Department did some basic studies on patients receiving the needling procedures. Four patients who received acupuncture treatment were relieved of pain or had some measure of increased mobility.

Assemblymen Gordon W. Duffy, Robert Moretti and Robert Monagan have introduced AB 1500 in order to permit medical schools to engage in scientific research and evaluation of acupuncture and other forms of traditional Chinese medicine. This legislation will have CMA endorsement and support. Assemblyman Duffy reconfirms this author's feeling that scientific investigation should be conducted in our medical schools to determine the validity of this type of practice.

A Letter on Acupuncture

Considerable nationwide publicity was given to a report that Thomas N. Elmendorf, M.D., President-elect of the California Medical Association, was relieved of pain following an acupuncture treatment at a meeting of the San Francisco Medical Society on May 9, 1972. Dr. Elmendorf has since received many letters of inquiry. For the information of its readers CALIFORNIA MEDICINE *publishes herewith a sample of the letter which Dr. Elmendorf has used in responding to these inquiries.*

Dear______________:

I am pleased to reply to your letter with regard to acupuncture and my experiences with it.

Here are the facts—

On May 9, two Chinese physicians placed two acupuncture needles along my lower right spine, one over my right hip and one just below my right knee on the outside of the upper leg. Some moxibustion was applied in the area of the right hip (moxibustion is the application of heat in various ways). The entire procedure took about 15 minutes and was relatively painless. I experienced a little deep pain with the application of the needle in the thigh and in the upper leg; however, only a small sharp pin-like sensation was felt along the lower spine.

When I arose from the table, the pain in my right hip was almost completely relieved. I was able to bear weight with hardly any pain. However, I am sorry to report to you that the relief of the pain lasted for only one hour. Following that, I was able to walk better for about two days, with less pain. After that period of time, my condition and pain have returned to the same level that existed prior to the acupuncture treatment.

Both of the Chinese physicians believe that they can cure my arthritis, which exists in both hips, with 10 to 15 acupuncture treatments. By "cure" they mean relief of pain and associated muscle spasms: they both deny that they can change the radiological picture of my arthritis. Both physicians have requested that I not give their names or addresses.

The problem is simply this. Acupuncture itself is a procedure in which the skin is penetrated, and as such must qualify as a medical, or perhaps, even surgical procedure. The Chinese physicians do not have licenses to practice medicine in the State of California or for that matter, anywhere in the United States or North America. Therefore, they are not licensed to perform acupuncture here, although acupuncture is not in itself illegal. A physician who had a license to practice medicine and surgery in the State of California, or in any of the states, who learned the procedure of acupuncture and wished to use it in his practice, could legally do so as long as he observed the ordinary prudence required of all medical practice.

I personally believe that acupuncture has some potential as a technique to relieve pain or even, perhaps, to induce anesthesia for surgical procedures. The truth of the matter is that Western medicine knows very little about acupuncture, and I believe that we should attempt to learn about it. Accordingly, university medical centers are being encouraged to attempt a scientific evaluation of acupuncture treatment. It may even be possible that enabling legislation will be required; however, we are exploring the situation in depth, and no doubt you will be reading more about it in the not too distant future.

I want to make it perfectly clear, that I do not endorse acupuncture at this time. I am sorry that some of the newspaper articles gave this impression.

It is only fair to report to you that a Chinese nurse, also part of the demonstration and who was reported to have had multiple disc disease with two surgeries, tells me that she has had complete relief of her pain for a period of four weeks.

I am immensely pleased that the medical profession here in California has such an open-minded attitude regarding this technique, about which we know very little; nor do we understand the traditional methods of Chinese medical practice.

I should mention that there are no physicians' names that I can give to you in the United States who practice acupuncture, although I have heard *rumors* that there are such physicians in Los Angeles, New York and Philadelphia. I want to reemphasize that this is rumor only.

My heart goes out to you, because I cannot do more for you; but if there is any value to the acupuncture treatment, we intend to find out.

THOMAS ELMENDORF, M.D.

Refer to: Waldron WG: The entomologist and illusions of parasitosis (Information). Calif Med 117:76-78, Aug 1972

The Entomologist and Illusions of Parasitosis

WILLIAM G. WALDRON, M.S., *Los Angeles*

The author has been involved in many cases where small to large groups of people in office buildings have said that they were being "bitten" by insects. Subsequent entomological investigations often rule out the presence of biting arthropods as the causative agent. This condition was recently identified for me by the local psychiatric profession as illusions of parasitosis, a phrase which encompasses many environmental and emotional factors. Unlike *de*lusions of parasitosis, which usually affects one person or a family,[1,2] *il*lusions of parasitosis can be evidenced by a heterogeneous group, with as many as 150 people believing that they are being "bitten" or "will be bitten." The unfortunate result of this is a sharp decrease in office efficiency and morale. In most cases, the condition is restricted to women employees. If there is a man in the office, he may grudgingly agree that there is a problem, but usually he is not affected. The people involved will often seek the help of a physician. As with delusions of parasitosis, there may be a "triggering" arthropod such as a flea infestation at home, or thrips in a bouquet of flowers. The person affected may then associate those bites with a situation at the office and transpose the problem from one environment to another. The itching is very readily transmitted to other employees, possibly by discussion, example, suggestion, or awareness. They in turn associate it with their own personal office problems. Those affected may greatly exaggerate their condition to draw attention from a supervisor.

Many times, sympathetic or efficiency-minded supervisors will employ a pest control operator

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to abate the "infestation." Experienced exterminators first check for the presence of an offending arthropod and, finding none, may treat the room or rooms (with the knowledge of the employer that it is unnecessary) simply to mollify the complainants. In some instances this technique works—at least temporarily. In most cases, however, the problem remains because the environmental conditions have not been changed.

The following are some environmental factors noted by the author as appearing to influence the possibility of illusions of parasitosis in an office. One or more may contribute to a situation:

- Crowded or cluttered working conditions.
- Routine, dull, or repetitious clerical work.
- The feeling of too much pressure.
- Too warm or too cold, perhaps owing to lack of proper air conditioning or central heating.
- Old or drab equipment and surroundings.
- Sedentary function.
- Handling or being exposed to foreign materials which might irritate the skin.

A typical request for help from an entomologist is for advice on the abatement of "telephone cable lice or fleas" or a "paper louse" infesting an office. In all cases it is necessary first to eliminate the possibility that an arthropod is the real cause. A few questions put to the complainants often help to clarify the issue:

- *Are you being bitten at home after changing clothes or showering?* The answer is usually negative; in other words, the problem is at the office.
- *What part of the body is being bitten?*
  - (a) Exposed parts of body, for example, hands, back of neck, forearm, face, legs?
  - (b) Front or back of lower leg, or both?
  - (c) How far up the leg?
  - (d) Covered or clothed parts of body?
- *Did you see the bug?* In many cases the affected persons indicate the insect is too small to be seen; but, individuals "know" they are being bitten by something.

The following are a few of the author's case histories which may graphically describe the different types of problems involved:

Case 1. Several women keypunch operators complained of being bitten on the forepart of their ankles and lower legs. Itching was confined to these areas. No arthropod was involved although fleas were suspected. Further investigation revealed that a fan directly in front of the machines blew small bits of tabulating cards, a side result of the keypunch operation, onto the legs of the women. The small pieces stuck into the mesh of their hose and set up a slight irritation when the leg moved. The girls scratched the area—and imagination, evidently, did the rest.

The fan was removed and the problem abated.

Case 2. Eight women worked at desks confined in a clutter of filing cabinets, business machines, and other equipment in a small windowless, drab room. The air was warm and stuffy. There was no unanimity among the affected employees as to the location of the bites. Only one woman had what appeared to be bites, and they were located around her ankles. Questioning disclosed that she had a recent flea infestation at her home but it had been abated. No other arthropod was involved.

A suggestion was made to the employers to rearrange the room, paint it, then decorate it with some attractive pictures and also to provide for better ventilation. This was done the following week-end and the itching and complaints ceased.

Case 3. Approximately 150 employees worked in a spacious, modern, and attractively decorated room. The employees, most of whom were women, took airline flight reservations by telephone. Observations of the entire operation showed a constant need for accuracy in dates, times, flights, and changing flight schedules—hence a feeling of pressure. In addition, at the front of the room, facing all the employees, was a darkened room attended by three people who monitored incoming calls and watched the employees.

The complaints were unanimous in that all women employees felt a tingling sensation and a slight "pulling" of their hose just above the ankle at the front part of the leg. Some felt "itchy" on other parts of their body. No men were affected. The morale and effectiveness of the employees was very low at the time of the investigation.

The company had tried to have a pest control operator treat the premises, but treatment had been refused because no arthropod could be found. However, all afflicted personnel still maintained that there was an infestation of "cable lice."

The employees worked in long, continuous rows. At the front part of the desk-like rows, immediately in front of their legs as they sat was an unshielded telephone cable. Apparently a static electric charge involving the women's nylon hose, the cable, and possibly the linoleum tile, was created and caused the pulling sensation of the hose.

Two suggestions, shield the cable and to keep the light on in the monitoring booth, were accepted and the problem abated.

There are no such creatures as cable lice, cable fleas, or paper lice. There is a limited array of arthropods which bite or sting people and these are predictable by their habitats, and to a certain extent by geographic distributions as well as defined habits and needs. The entomologist's role with illusions of parasitosis is first to attempt to determine what is real. After ruling out biting insects, he may try to find some other causative agent or agents in the immediate environment.

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CLINICAL CARDIOLOGY SERIES

Cardiac Tamponade and Constrictive Pericarditis

Part I—Diagnosis

Ralph Shabetai, M.D.

Material Supplied by the American Heart Association

The intrapericardial pressure in normal persons is subatmospheric. Cardiac tamponade exists when the intrapericardial pressure is appreciably increased by fluid. Its severity depends upon the rate of accumulation and the volume of pericardial fluid. Important causes include trauma, infection and ruptured aortic aneurysm or myocardial infarction.

Equal compression of all cardiac chambers by the fluid explains the clinical picture: elevated venous pressure, pulmonary congestion, hypotension and a quiet heart. One or two hundred milliliters of fluid accumulated rapidly can cause tamponade, as in trauma. In infectious and malignant effusions the onset, although less acute, may still be rapid. If an effusion collects over many days or weeks, several hundred milliliters may gather before tamponade ensues.

In extreme cases, clinical examination discloses impaired cerebral function, pallor, sweating, and impalpable or weak radial pulses. Cerebral symptoms are less prominent with milder tamponade but the patient may note chest discomfort and dyspnea.

Pulsus paradoxus, an abnormal inspiratory fall in arterial pressure, is almost invariable with tamponade. The pulse diminishes or entirely disappears during each inspiration. Pulsus paradoxus may be difficult to elicit under three circumstances: profound hypotension, mild tamponade, and tachypnea. When the radial pulse is impalpable, paradoxus may be elicited from the femoral pulse. To appreciate pulsus paradoxus in mild cases, it may be necessary to have the patient breathe as deeply and slowly as possible without straining at end inspiration or expiration. However, when the aim is to measure the severity rather than simply detect pulsus paradoxus, respiration should be maintained as normal as possible, because hyperventilation exaggerates pulsus paradoxus. Blood pressure is measured with a cuff, releasing the pressure as slowly and evenly as possible. Initially, systolic sounds are audible only during expiration, but as cuff pressure falls, a point is reached when the sounds are heard throughout the respiratory cycle. The pressure difference between these two points estimates pulsus paradoxus.

Elevated venous pressure is best observed with the thorax elevated, frequently to 90 degrees. Venous pulsations are visible inferior and anterior to the ear and display a single slow expansion followed by a rapid collapse synchronous with the carotid pulse. Normal inspiratory variation and fall in venous pressure is often maintained. Precordial activity is absent or diminished, but if the apex beat is palpable cardiac

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This article is to be published in two parts. Part II will appear in a subsequent issue.

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dullness may be percussed lateral to it. The heart sounds are usually normal, sometimes muffled. A pericardial friction rub may be heard. It does not preclude effusion. The electrocardiogram may show sinus tachycardia, decreased voltage, elevated ST segments and, in severe cases, electrical alternans. The chest roentgenograph often reveals a globular increase in the cardio-pericardial silhouette with disproportionately clear lung fields. If conditions permit fluoroscopy, it will be observed that the cardiac borders hardly pulsate while the aortic pulsations are vigorous. Hilar vessel shadows are often obliterated.

The presence of pericardial effusion can be confirmed most conveniently and safely by echocardiography. When this facility is not available, special radiological procedures such as intravenous CO_2 injection or angiocardiography may be employed.

Constrictive Pericarditis

In constrictive pericarditis the heart is compressed not by fluid but by the visceral pericardium. In the majority of cases all cardiac chambers are equally involved and this explains the hemodynamic similarities to tamponade. Intrapericardial pressure cannot vary during the respiratory and cardiac cycles because the pericardial space is obliterated. This explains the differences from tamponade. The cause is unknown in most instances, tuberculosis being much less common than formerly. Other important causes include malignant disease, therapeutic radiation, collagen diseases and infections.

Chronic constrictive pericarditis develops insidiously over many years. The pericardium often becomes heavily calcified. In recent series, many cases are subacute and develop in weeks or months, a difference which reflects the changing etiologic pattern.

Patients with chronic constrictive pericarditis frequently are cachectic, pale, mildly jaundiced and cyanotic. The venous pressure is greatly elevated and the arterial pulse pressure may be small, although pulsus paradoxus occurs in only a third of the cases. The venous pulse displays two rapidly collapsing waves, one in systole, the other in diastole. The pronounced diastolic collapse may help to differentiate this condition from tamponade. The positive filling waves are much less prominent. The normal decrease in venous pressure with inspiration is absent and paradoxical expansion may be seen.

Elevated venous pressure, hepatic and renal underperfusion and congestion, and protein-losing enteropathy combine to make edema, often with disproportionate ascites, a prominent feature of the disease. The liver may be enlarged or cirrhotic and its function severely impaired.

Precordial activity is absent or decreased. Sometimes systolic retractions are found. A loud protodiastolic third heart sound is heard all over the precordium. The electrocardiogram may show wide bifid P waves until atrial fibrillation supervenes. QRS voltage is decreased and the T wave is inverted in most leads. The heart appears normal in size to moderately enlarged on chest roentgenographs. Calcification may be seen readily on plain chest films, especially in the lateral projection. Thus the radiologist may be the first to call attention to the correct diagnosis. Fluoroscopy confirms calcification and reveals decreased amplitude of motion of the heart walls.

Cachexia, anasarca, liver failure and a high venous pressure constitute a striking clinical picture. Nevertheless, the diagnosis is often missed because the patient is considered to have heart failure or primary liver disease. However, the venous pressure is normal in non-cardiopericardial causes of edema. If the pericardium is not calcified, final distinction from myocardial disease may require cardiac catheterization.

In subacute cases there is less cachexia and liver damage. One can often obtain a history of recent acute pericarditis or chest trauma. The pericardium is not calcified and pulsus paradoxus is more common than in the chronic form. The diagnosis should be suspected in any patient with unexplained weight gain, dyspnea, edema, hepatomegaly and raised venous pressure who does not have heart disease of easily recognized cause.

(Continued in Part II to be published in a subsequent issue)

In Memoriam

ACH, BERT, Los Angeles, Died June 2, 1972 in Los Angeles of heart disease, aged 49. Graduate of College of Osteophathic Physicians and Surgeons, Los Angeles, 1957. Licensed in California in 1958. M.D. degree from California College of Medicine, 1962. Doctor Ach was a member of the Los Angeles County Medical Association.

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ASHER, JOHN CURTIS, San Diego. Died June 21, 1972, aged 56. Graduate of Tulane University School of Medicine, New Orleans, 1941. Licensed in California in 1948. Doctor Asher was a member of the San Diego County Medical Society.

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BARROWS, CHARLES V., Bakersfield. Died February 10, 1972 in Knoxville, Iowa of heart disease, aged 81. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1931. Licensed in California in 1943. Doctor Barrows was a member of the Kern County Medical Society.

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BAUGHMAN, WILLIAM HENRY, Alameda. Died May 29, 1972 in Oakland of cerebral vascular insufficiency, aged 88. Graduate of the University of Virginia School of Medicine, Charlottesville, 1910. Licensed in California in 1924. Doctor Baughman was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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COLEMAN, BARNEY E., San Luis Obispo. Died March 24, 1972 in San Luis Obispo of normochromic, normocytic anemia, aged 82. Graduate of College of Physicians & Surgeons, Medical Department, University of Southern California, 1915. Licensed in California in 1915. Doctor Coleman was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

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DAWSON, GEORGE I., Napa. Died June 18, 1972 of heart disease in San Francisco, aged 79. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1922. Licensed in California in 1922. Doctor Dawson was a member of the Napa County Medical Society.

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FREEMAN, WALTER, San Francisco. Died May 31, 1972 in San Francisco of cancer, aged 76. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1920. Licensed in California in 1953. Doctor Freeman was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

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HIXON, WILLIAM CARTER, JR., Beverly Hills. Died June 13, 1972 in Los Angeles of heart disease, aged 71. Graduate of Baylor University College of Medicine, Houston, 1928. Licensed in California in 1930. Doctor Hixon was a member of the Los Angeles County Medical Association.

HOPKINS, HELEN L., Los Angeles. Died May 20, 1972 in Los Angeles, aged 73. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1925. Licensed in California in 1930. Doctor Hopkins was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

JOHNSON, DAVID E., Santa Clara. Was killed May 31, 1972 in an automobile crash near Custer, South Dakota, aged 47. Graduate of the Medical College of Georgia, Augusta, 1949. Licensed in California in 1955. Doctor Johnson was a member of the Santa Clara County Medical Society.

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LEHRER, HARRY, Los Angeles. Died June 26, 1972 in Los Angeles of a stroke, aged 67. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1938. Licensed in California in 1938. M.D. degree from California College of Medicine, 1962. Doctor Lehrer was a member of the Los Angeles County Medical Association.

⁂

NICHOLS, J. NORTON, Los Angeles. Died June 18, 1972 in Los Angeles, aged 80. Graduate of Vanderbilt University School of Medicine, Nashville, 1914. Licensed in California in 1920. Doctor Nichols was a member of the Los Angeles County Medical Association.

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NIEHAUS, RALPH F., San Diego. Died May 23, 1972 in San Diego, aged 67. Graduate of University of Cincinnati College of Medicine, 1932. Licensed in California in 1943. Doctor Niehaus was an associate member of the San Diego County Medical Society.

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RESPINI, CHARLES JOHN, Palo Alto. Died May 16, 1972 in San Jose of heart disease, aged 51. Graduate of the University of California, Berkeley-San Francisco, 1944. Licensed in California in 1947. Doctor Respini was a member of the Santa Clara County Medical Society.

⁂

RUDIS, JAMES ANTHONY, Belmont. Died June 15, 1972 in Chico, aged 64. Graduate of Queen's University Faculty of Medicine, Belfast, 1960. Licensed in California in 1963. Doctor Rudis was a member of the San Mateo County Medical Society.

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WAGGENER, HEWITT A., Los Angeles. Died May 21, 1972 in Los Angeles of leukemia, aged 92. Graduate of Creighton University School of Medicine, Omaha, 1904. Licensed in California in 1914. Doctor Waggener was a member of the Los Angeles County Medical Association.

Refer to: Geokas MC, Olsen H, Swanson V, et al: The association of viral hepatitis and acute pancreatitis. Calif Med 117:1-7, Sep 1972

California Medicine
THE WESTERN JOURNAL OF MEDICINE

The Association of Viral Hepatitis and Acute Pancreatitis

MICHAEL C. GEOKAS, M.D., PH.D., HARVEY OLSEN., M.D., VIRGINIA SWANSON, M.D., AND HEINRICH RINDERKNECHT, PH.D., *Los Angeles*

■ *The histological features of 24 pancreases obtained from patients who died of causes other than hepatitis, pancreatitis or pancreatic tumors, included a variable degree of autolysis, rare foci of inflammatory reaction but no hemorrhagic fat necrosis or destruction of elastic tissue in vessel walls (elastolysis). Assays of elastase in extracts of these pancreases showed no free enzyme, but varying amounts of proelastase.*

A review of autopsy findings in 33 patients with fatal liver necrosis attributed to halothane anesthesia, demonstrated changes of acute pancreatitis only in two. On the other hand, a review of 16 cases of fulminant viral hepatitis revealed changes characteristic of acute pancreatitis in seven — interstitial edema, hemorrhagic fat necrosis, inflammatory reaction and frequently elastolysis in vessel walls. Determination of elastase in extracts of one pancreas showed the bulk of the enzyme in free form. Furthermore, assays of urinary amylase in 44 patients with viral hepatitis showed increased levels of this enzyme (2583 ± 398 mean value ± standard error, Somogyi units per 100 ml in 13, or 29.5 percent).

The evidence suggests that acute pancreatitis may at times complicate viral hepatitis. Although direct proof of viral pancreatic involvement is not feasible at present, a rational hypothesis is advanced which underlines similar mechanisms of tissue involvement in both liver and pancreas that may be brought about by the hepatitis viruses.

THE CONCEPT THAT VIRAL HEPATITIS is a generalized disease is an old one and has recently been stressed again.[1] The extrahepatic effects of the hepatitis virus include the blood and hemopoietic tissues, the mucosa of the stomach and small intestine and the kidneys. Myocarditis[2] and acute hemorrhagic necrosis of the bowel[3] have also been noted in autopsy material of fulminant cases. Whereas a few scattered reports of acute pancreatitis[4-7] complicating acute viral hepatitis have been published, most surveys of the latter

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condition do not mention acute pancreatitis as one of its complications.[8-11]

On the other hand among the various reviews on pancreatitis, only two[12,13] mention the viruses of acute hepatitis as possible etiologic factors.

In this paper seven cases of acute pancreatitis concurrent with fulminant viral hepatitis will be presented, and a rational hypothesis will be advanced concerning a possible common initiating mechanism of tissue destruction, caused by the virus, in both the liver and pancreas.

Materials and Methods. All patients reported here came from the Los Angeles County-USC Medical Center.

Control Series. The pancreases of 24 subjects who died from causes other than hepatitis, pancreatitis or pancreatic tumors were removed as soon as possible after death and tissue was fixed and subsequently stained with hematoxylin-eosin and Verhoeff's hematoxylin for histological studies. Furthermore, samples from the head and tail of the pancreas were frozen to −20°C and subsequently assayed for free elastase and total elastase activity (following activation with bovine trypsin) using a sensitive spectrophotofluorimetric method developed in this laboratory.[14]

Hepatic necrosis associated with halothane. The pancreatic histological changes of 33 patients who died with hepatic necrosis attributed to more than one exposure to halothane anesthesia, were reviewed. These cases constituted part of a recent report from the same institution.[15]

Fulminant Viral Hepatitis. Sixteen cases of fatal viral hepatitis in which autopsy was done between 1958 and 1967 were reviewed. Pancreatic tissue sections stained routinely with hematoxylin-eosin were described, in most of the cases, as representing "pancreatic autolysis." Several new sections of wet pancreatic tissue were stained with hematoxylin-eosin and Verhoeff's hematoxylin for re-evaluation. Moreover in one of these cases (Case 1 in following report) in which fresh pancreatic tissue was obtained 12 hours after death, assays of free and total elastase activity were carried out in extracts from the head, body and tail of the pancreas.

Results

Control series. Sections of tissue from 24 pancreases obtained up to 48 hours after death showed autolysis of parenchyma of a varying degree and rare foci of inflammatory reaction, but no hemorrhagic fat necrosis or destruction of elastic tissue (elastolysis) in vessel walls. Furthermore in 48 extracts from head and tail of these pancreases no free elastase was found but varying amounts of proelastase were detected (53 ± 32 and 47 ± 24 μg per gram of wet tissue, mean values ± standard error, for the head and tail respectively).

Hepatic necrosis associated with halothane. Acute pancreatitis was found in two out of the 33 cases of fulminant hepatitis attributed to more than one exposures to halothane anesthesia:

In one of those cases the patient was a 45-year-old woman who was in hospital because of vaginal bleeding. Dilation and curettage was carried out and three units of whole blood were transfused. Four weeks later she was readmitted and had an abdominal hysterectomy for submucosal uterine fibroids. Six days after operation jaundice developed, with fever, and her condition progressively deteriorated. Prothrombin time was 19 percent of control, total serum bilirubin 11.2 mg per 100 ml., SGOT 4,500 and SGPT 5,800 units. The patient died 19 days after last admission. At autopsy the liver was found to be shrunken, weighing 890 grams. Microscopic examination revealed extensive necrosis of liver cells with a thin rim of parenchyma remaining about portal structures. The pattern was indistinguishable from that of viral hepatitis. Pancreatic sections showed acute pancreatitis with edema, small hemorrhages and foci of parenchymatous necrosis.

In the other case, a 62-year-old man had cholecystectomy for cholelithiasis. Sixteen days later he was operated upon again, for drainage of a subhepatic hematoma. Following this he became jaundiced and his condition deteriorated. He had cardiac arrest twice, with resuscitation, and died the fifth postoperative day. Microscopic examination of liver sections in this case showed changes compatible with toxic hepatic necrosis. On examination of pancreatic sections, acute inflammation with edema and small hemorrhages and foci of necrosis of the parenchyma were noted. In most of the remaining 31 patients the pancreas was normal with a variable degree of autolysis. In a few cases rare foci of inflammatory reaction and fat necrosis were present.

Fulminant Viral Hepatitis. All 16 pancreases in the fulminant viral hepatitis group were removed from 8 to 48 hours postmortem. The histological picture in nine was identical with that observed in the control series, except for somewhat more extensive autolysis. In the remaining seven however, histological features characteristic of acute pancreatitis were observed—congestion of blood vessels, thrombosis, interstitial edema, hemorrhagic fat and parenchymatous necrosis, inflammatory reaction and frequently destruction of elastic fibers in vessel walls. Assays of free elastase and proelastase in extracts from the head, body and tail of the pancreas in Case 1 (reported below) showed that the bulk of the enzyme existed in the free form.

The clinical history, course, laboratory data and autopsy findings of each of the seven cases reported here is given in the following case reports.

Case 1. A 38-year-old white woman was admitted to hospital, following exposure to a patient with hepatitis six weeks before her admission in February 1967, because of a two-week history of deepening jaundice. A two-week interval of anorexia, nausea and epigastric discomfort, preceded the period of overt jaundice.

During the past year the patient had felt tremulous and nervous, and five days before admission her private physician diagnosed hyperthyroidism but no treatment was initiated. On physical examination blood pressure was 150/70, pulse rate 118, respirations 20 per minute, and temperature 98.2°F rectally. The patient was nervous, hyperactive and deeply jaundiced but in no distress. The liver was palpable 5 cm below the costal margin and the spleen was not palpable. Hemoglobin was 12.4 grams per 100 ml of blood, leukocytes numbered 8,900 per cu mm with normal differential, total serum bilirubin was 32 mg per 100 ml with 7 mg per 100 ml direct form. Alkaline phosphatase was 3.5 Bodansky units, SGOT 740 units and, SGPT 650 units per 100 ml, and prothrombin time within 5 percent of the control. Protein-bound iodine was 12.1 mcg per 100 ml and T_3 uptake was 22.2 percent. By the second hospital day the patient was quite confused, with asterixis easily demonstrable. She was given intravenous glucose and hydrocortisone sodium succinate. She continued to deteriorate rapidly and on the fifth hospital day she was started on propylthiouracil 400 mg daily. By the end of the fifth hospital day the patient was obtund and had hypotension, oliguria and Cheyne-Stokes respiration. Subsequently spontaneous respirations ceased and resuscitation was unsuccessful.

At autopsy the liver weighed 1000 grams. In microscopic sections there was massive necrosis that had destroyed some lobules almost completely. The necrosis was primarily centrolobular in type, with collapse of the stroma and infiltration with round cells and pigment-filled macrophages. The pancreas was edematous and hemorrhagic, with areas of fat necrosis throughout the entire gland. There was hemorrhage into the retroperitoneal tissues. Histological sections showed interstitial hemorrhage, extensive parenchymatous necrosis, fat necrosis and inflammatory reaction. There was destruction of vessel walls including almost complete disappearance of elastic tissue ("ghost vessels") and thrombosis.

Comment. This case of fulminant viral hepatitis had associated acute hemorrhagic pancreatitis which was unsuspected during life. It is possible that the circulatory and metabolic effects of the coexisting hyperthyroidism enhanced tissue destruction in both the liver and the pancreas.

Case 2. A 41-year-old white man, known to be an alcoholic and a heroin addict, was admitted on July 16, 1961, because of severe burns (second degree of face and arms, third degree of back). Five days later, while still in hospital, the patient attempted suicide by slashing his wrists. He was transfused with one unit of blood and one unit of fresh plasma. Eight days later he received one more unit of blood and two of plasma. Six weeks following his first blood and plasma transfusion he was readmitted because of nausea, vomiting, fever and diarrhea. On physical examination blood pressure was 105/50 mm of mercury, temperature 40°C (104°F), pulse 110 and respirations 30 per minute. He appeared acutely ill, toxic and icteric. The liver was palpable 4 cm below the costal margin and the tip of the spleen was easily felt. Serum bilirubin was 7.3 mg per 100 ml with 3.4 mg direct form. Hemoglobin content was 13.6 grams per 100 ml of blood and leukocytes numbered 40,500 with 51 percent band and 44 percent segmented forms. SGOT was 2,520 units and serum amylase 5,500 Somogyi units. Blood was pH 7.19, serum CO_2 (bicarbonate) 6 mEq, ml, potassium 6.5 mEq, and sodium 135 mEq per liter, and BUN 18 mg per 100 ml. Prothrombin time within 5 percent of the control. The patient was treated with corticosteroids, fluid and electrolyte replacement. Despite vigorous treatment his condition worsened, with deepening jaundice and hypotension, and he died five days after onset of the febrile-icteric episode. At autopsy, there was extensive necrosis of liver cells with only reticulum remaining. Periportal round cell infiltrates and occasional focal hemorrhages were found. Sections of the pancreas showed patchy parenchymatous necrosis, including destruction of elastic tissue of vessel walls and hemorrhagic fat necrosis.

Comment. This is also a case of fulminant hepatitis with severe acidosis and concomitant acute pancreatitis in an alcoholic and heroin addict who had received blood and plasma transfusions six weeks before the jaundice appeared.

Case 3. A 25-year-old white woman was admitted on October 23, 1959, with a history of having delivered a normal male infant six weeks previously. During the three-week postpartum period she felt well; then she began to have fever, chills, nausea, vomiting, malaise, black stools and dark urine. She denied recent blood transfusions or other injections, except for the routine procedures at the time of delivery. On physical examination, blood pressure was 114/60 mm of mercury, temperature 37°C (98.6°F), pulse 104, respirations 28. Skin and sclerae were icteric. A plain film of the abdomen showed moderate ileus. Hemoglobin was 13.2 grams per 100 ml, white blood cell count 27,600 per cu mm with 77 segmented, 12 band forms and 11 lymphocytes. Blood urea nitrogen was 4 mg and blood sugar 71 mg per 100 ml. Potassium was 3.9 mEq and CO_2 (bicarbonate) 31 mEq per liter, bilirubin 34.5 mg per 100 ml total, SGOT 590 units, SGPT 202 units, alkaline phosphatase 4.8 Bodansky units, prothrombin time 9 percent of control and serum calcium 8.5 mg per 100 ml. The patient's course was characterized by progressive icterus and coma with repeated attacks of generalized convulsions. Treatment consisted of intravenous fluids, corticosteroids and antibiotics. She gradually lapsed into coma, became hypotensive and died seven days after admission.

At autopsy the liver weighed 900 grams and had gross and microscopic features characteristic of acute necrosis of viral origin. The pancreatic parenchyma was dark red in cross-sections and the peripancreatic tissue was hemorrhagic, with areas of fat necrosis. Microscopically, parenchymatous necrosis with elastolysis in vessel walls, thrombosis and interstitial hemorrhage were seen.

Comment. This is again a case of fulminant hepatitis with concomitant pancreatitis which was unsuspected before death. The paralytic ileus, the hypocalcemia and progressive hypotension, without signs of gross gastrointestinal bleeding, constitute the only indication of pancreatic involvement. However, reevaluation of the pancreatic sections revealed parenchymatous necrosis, elastolysis, thrombosis and focal interstitial bleeding.

Case 4. A 55-year-old white woman with known diabetes was first admitted on February 15, 1959, in diabetic coma. At that time she received two units of plasma. Two weeks before, she had complained of severe epigastric distress, and a week before entering the hospital she had noticed jaundice and dark urine. On physical examination, the blood pressure was 120/60 mm, the temperature 37.9°C (100.2°F), pulse rate 105, and respirations 27 per minute. There was considerable epigastric pain on palpation. The serum bilirubin was 25.5 mg total, alkaline phosphatase 10 Bodansky units, prothrombin time 33 percent of control, hemoglobin 13.0 grams per 100 ml, white blood cell count 5,900 per cu mm with a normal differential, and serum SGOT 3,900 units. The patient lapsed into coma the fifth day and died on the seventh day after admission.

Postmortem liver sections showed widespread parenchymatous destruction with many eosinophilic cell shadows. There was also ductal proliferation and infiltration by lymphocytes and macrophages. Sections of the pancreas were initially read as representing "pancreatic autolysis." However, reevaluation of sections showed diffuse changes of acute pancreatitis.

Case 5. An 8-year-old Negro boy was admitted May 18, 1959, because of deepening jaundice of ten days' duration and nausea with vomiting for three days. Anorexia and fatigue were noticed for two weeks before the jaundice appeared. On physical examination, the temperature was 37.8°C (100°F), pulse rate 98, respirations 24. The liver was palpable about 4 cm below the costal margin and there was questionable splenomegaly. Petechiae were noted in both lower extremities. Hemoglobin was 10.5 grams per 100 ml of blood, serum bilirubin 21.5 total mg per 100 ml, alkaline phosphatase 8.4 Bodansky units. The patient's condition deteriorated progressively, with epistaxis, coffee-ground emesis and deepening coma. He died six days after admission.

At autopsy, almost complete hepatic necrosis with only ghost-like remnants remaining was noted. There were islands of hemorrhage and questionable acidophilic bodies. Pancreatic sections showed acute hemorrhagic pancreatitis.

Case 6. A 2-year-old child was admitted July 19, 1967, because of jaundice and coma of three days' duration. The patient had been healthy until June 15, when vomiting, diarrhea and fever developed, followed by dark urine and jaundice. He was admitted to hospital elsewhere for nine days and then was discharged for care at home.

On physical examination July 19, blood pressure was 100/60 mm, pulse 100, temperature 38.3°C (101°F), respirations 32. The child was jaundiced and in coma. The liver was felt 4 cm below the right costal margin. The spleen was palpable. Hemoglobin content was 9.5 grams per 100 ml of blood, white blood cells 18,800 per cu mm, BUN 6 mg per 100 ml, sodium 139, potassium 4.0, and CO_2 (bicarbonate) 26.0 mEq per liter, bilirubin 20.7 mg per 100 ml (direct 12.6 mg, indirect 8.1 mg), SGOT 860 units, SGPT 2060 units, and alkaline phosphatase 5.4 Bodansky units. Prothrombin time was within 10 percent of control. Despite vigorous supportive treatment, the patient died the fourth day in hospital.

At autopsy, centrolobular hepatic necrosis and acute hemorrhagic pancreatitis were present.

Case 7. A 30-year-old Caucasian woman was admitted January 30, 1966, because of jaundice that had appeared four weeks before. She had been admitted first to another hospital, where serum transaminase of 2,500 units and total serum bilirubin of 25 mg per 100 ml were noted. (Incident to hysterectomy in November of 1965 the patient had received four blood transfusions.) She improved somewhat and was discharged to her home. Five days later she lapsed into coma and was admitted to the Los Angeles County Medical Center. Despite vigorous treatment including corticosteroids and exchange transfusions she died four days after admission. At autopsy, centrolobular hepatic necrosis and acute hemorrhagic pancreatitis were found.

Comment. Cases 4, 5, 6, and 7 represent examples of viral hepatitis associated with acute pancreatitis. However, serum amylase and urinary diastase were not determined during the stay in hospital.

Discussion

The results of the present investigation support the findings of Joske,[7] who emphasized that the viruses of acute hepatitis in man may occasionally cause pancreatitis. In our study, the detection of pancreatic involvement, which occurred in seven of sixteen cases of fulminant viral hepatitis, was accomplished by comparing certain distinct histological features of acute pancreatitis (developing as a complication of viral hepatitis) with the changes observed in the pancreas of 24 patients who died of causes other than hepatitis or pancreatitis. In both groups, pancreatic tissue was obtained up to 48 hours postmortem. It is interesting that in all cases included in this report, pancreatic involvement was unsuspected during life, except in Case 2 in which elevated serum amylase was observed. Furthermore, the existence of acute pancreatitis was not appreciated at autopsy except in Case 1, in which several sections of pancreatic tissue were stained with both hematoxylin-eosin and Verhoeff's-hematoxylin stains (the latter for the identification of elastolysis in vessel walls), and in Case 2 in which acute pancreatitis was suspected antemortem. Thus, the hemorrhagic fat necrosis, the inflammatory reaction, and the destruction of elastic fibers in the walls of intrapancreatic vessels, were the main features of pancreatic involvement in sections of tissue obtained from seven patients with fulminant viral hepatitis and were conspicuously absent from sections of 24 pancreases of the control group. Free elastase activity was detected in two pancreatic extracts from Case 1, whereas such activity was absent from 48 extracts of the control series. On the other hand, among the 33 patients with fatal hepatic necrosis, following halothane anesthesia, only two cases of acute pancreatitis were found. However, the first patient had received three units of whole blood four weeks before his last exposure to halothane and the microscopic liver changes were indistinguishable from those seen in fulminant viral hepatitis. The second patient underwent cholecystectomy for acute cholecystitis, followed by another exploration for subhepatic hematoma and the possibility of postoperative pancreatitis cannot be excluded.

When acute pancreatitis complicates fulminant viral hepatitis, the following possibilities exist concerning the pathogenesis of pancreatic changes:

Involvement of the pancreas by the virus of hepatitis

Intrapancreatic hemorrhage due to hypoprothrombinemia, with resultant acute pancreatic necrosis; hemorrhagic pancreatitis is known to occur as a complication of anticoagulant therapy.[16] However, excessive interstitial hemorrhage which is characteristic of drug-induced hypoprothrombinemia-pancreatitis was not observed in these series.

Acute pancreatitis due to corticosteroids, in view of the fact that some of the patients (Cases 1, 2, 3, and 7) received hydrocortisone sodium succinate intravenously. It is known that corticosteroid treatment, even for a few days, might produce mild, focal pancreatitis.[17] However, all cases included in this report showed diffuse changes of acute pancreatitis, three of them hemorrhagic (Cases 1, 5, and 6).

It is conceivable that acute pancreatitis associated with viral hepatitis is due to a direct involvement of the pancreas by the hepatitis viruses. However it is realized that conclusive evidence of viral pancreatic involvement cannot be obtained at the present time. Such an accomplishment must await refinements in specific diagnosis of viral hepatitis and isolation of the causative viruses in animal tissues. Acute pancreatitis is known to occur in man as a complication of infectious mononucleosis[18,19] and mumps,[20] and has been observed in animals infected with the encephalomyocarditis,[21] coxsackie Group B[22] and the foot and mouth disease viruses.[23] It is noteworthy that recent histochemical and biochemical evidence suggests early changes in liver lysosomes, preceding necrosis in murine[24,25] as well as in human viral hepatitis,[26] in the latter case with an early rise of serum b-glucuronidase together with a rise in transaminase.[27] Recent biochemical evidence also suggests increased permeability of lysosomal membranes in cells infected with various types of cytopathic viruses.[28] One might speculate, therefore, that the release of lysosmal hydrolases in liver or pancreatic cells infected by a virus, may bring about cytolysis and, in the case of the pancreas, activation of zymogens of exportable enzymes.[29] The mechanism by which a virus might increase the permeability of the lysosomal membrane is unknown; it has been suggested that the integrity of this membrane is maintained by an ATP-ase enzyme complex and the labilizing effect of a virus may be due to a direct or indirect effect of ATP-ase.[30]

TABLE 1.—*Reported Cases of Fatal Hepatitis Associated with Acute Pancreatitis*

Author and Ref	*Year*	*Number of Cases*	*Age (years)*
Saint, EG and Weiden, S[12]	1953	1	"middle aged woman"
Joske, RA[7]	1955	3	44, 52, 69
Achord, JL[1]	1968	2	7,19,
Geokas, et al.	1971	7	2, 8, 25, 30, 38, 41, 55

Despite the fact that only 13 fatal cases of fulminant viral hepatitis associated with acute pancreatitis have been reported to date (Table 1) one would suspect that this represents only the apex of an iceberg and that the true incidence of pancreatitis, of a variable degree of severity, in both the fatal and nonfatal forms of hepatitis may be appreciable. During a study with acute hepatitis volunteers[31] it was noticed that a number of them experienced symptoms indistinguishable from those of acute pancreatitis, such as acute severe epigastric pain radiating through to the mid-back. In two such cases, moderate elevations of serum amylase and lipase were noted. Studying a group of 14 patients with viral hepatitis Cummins and Bockus[32] found increased levels of serum amylase in three out of fourteen and of lipase in two out of twelve who were tested. Furthermore, a prospective study is now in progress in this laboratory, which among other tests includes determinations of urinary amylase in all patients with viral hepatitis. Preliminary data from 44 such patients have shown that 13 of them (29.5 percent) had increased urinary amylase[33] levels (range 1350 to 5900 Somogyi units per 100 ml or 2583 ± 398, mean value ± standard error). In the remaining 31 patients of this group urinary amylase ranged from 143 to 1130 Somogyi units per 100 ml (684 ± 56 mean value ± SE). On the other hand in 44 control subjects the values of urine amylase ranged between 50 to 1120 Somogyi units per 100 ml (467 ± 47 mean value ± SE).

It must be realized, that increased urinary levels of amylase in the course of viral hepatitis might be due to the following causes: (a) concomitant pancreatitis, (b) derangement of a control mechanism of amylase metabolism normally exercised by the liver or an efflux of abnormal amounts "of liver amylase."[34,35] In a recent report acute pancreatitis was found at autopsy in two patients who died of fulminant viral hepatitis; paper electrophoresis of serum and urine from one of these patients revealed migration patterns of amylolytic activity identical to those of saline extracts of human pancreas.[36]

At present, it seems reasonable to suggest that in all cases of viral hepatitis, clinical laboratory or autopsy evidence of coexisting pancreatitis should be diligently sought. Moreover, some prognostic and therapeutic implications stemming from the association of two conditions appear pertinent. Even mild forms of pancreatic involvement may aggravate the clinical picture of hepatitis, with epigastric pain, hypovolemia and hypotension and may require vigorous replacement therapy and measures (for example, nasogastric suction) appropriate to the management of acute pancreatitis. Acute hemorrhagic pancreatitis, will of course constitute a formidable complication of fulminant hepatitis by adding new circulatory and biochemical disturbances, to a disease which by itself carries a poor prognosis. Furthermore, the question arises, if the treatment of such patients with exchange transfusions,[37] employing large amounts of heparinized blood should be advocated (Case 7). Each unit of infused plasma contains approximately 20 mg of heparin and the iatrogenic coagulation defect is compounded by the severe bleeding diathesis due to massive impairment of liver function. Although, the possibility of intrapancreatic and retroperitoneal bleeding will exist in such cases, it is known that heparin inhibits the activity of trypsin[38] and has been used in the treatment of experimental pancreatitis with beneficial results.[39]

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Peritonitis from Starch Glove Powder

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■ *Contamination of surgical wounds by starch glove powders has produced peritoneal inflammation and adhesions in many patients. Some have required surgical operation because of possible infection, others because of obstruction of the intestine. Resolving granulomas and fibrosis have been observed as incidental asymptomatic lesions in some patients during reoperation for other conditions.*

Starch granules are probably capable of producing inflammation in any patient, and the degree is believed to be related to the amount of starch present.

Care in removing glove powder from gloves before they are worn in an operation will diminish or eliminate the problem. Removal can be accomplished by rubbing the gloves with a moist sterile towel or laparotomy tape.

Powdered corn starch, which had recently been introduced as a lubricant for surgical gloves,[1,2] was identified as a cause of granulomatous peritonitis in 1956.[3] Subsequently, a few cases have been reported almost every year, but there has been no indication of numerous cases in all parts of the United States.

In 1970, we circulated a notice in several journals of pathology requesting data and tissue slides from such cases; furthermore, direct inquiry was made of two pathologists[4,5] who had published brief abstracts of such cases. Communications were received from 37 pathologists, most of whom had from one to three cases; 15 were submitted by one pathologist and are included here, and 13 more accumulated by another pathologist are to be reported separately.

Information came from 15 states ranging from Maine to Hawaii and from Minnesota to Texas; data were adequate and tissue slides were available for study from 52 cases (including seven of our own), and these are the basis of this report.*

It has been possible to sharply define the clinical entity and to elucidate the evolution of the lesions over a long period. Tissues were obtained from patients as early as nine days and as late as four years after the introduction of starch into the peritoneal cavity. No other series has been so large, nor has the sequence of pathological changes from such early lesions to old completely fibrotic ones previously been reported.

Clinical Description:

All cases followed abdominal operation, with one exception. The latter occurred after vaginal examination during which the powder was presumably introduced through the uterine tubes, as described by other investigators.[6]

The ages of the patients varied from 22 to 78 years. There were 43 women and nine men, the

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*The following pathologists contributed information and tissue slides for this study (number of cases from each indicated in parentheses): RC Boylan MD (1), R Campbell MD (1), JK Duckworth MD (2), RE Fechner MD (1), C Robes MD (1), L Goodman MD (2), RC Harsch MD (2), HL Hoffman MD (1), CT Kelso MD (1), R Kleinhenz MD (1), WD Moore MD (3), C Moran MD (1), MJ Pophal MD (3), AC Pratt MD (1), H Standage MD (1), RE Swanson MD (3), CN Tschetter MD (3), EE Tueller MD (15), AS Ullman MD (1), JK Waken MD (1).

disparity reflecting in part the fact that a large proportion of abdominal operations are directed at the female genitalia; in this series, 22 of the 52 primary procedures were of this type. Gallbladder operations were also frequent, and nine of the 14 cholecystectomy patients were women.

In general, there were two different patterns, both clinically and pathologically. There were 34 early cases, those in which symptoms occurred and a second operation was performed within two months after the introduction of starch into the peritoneal cavity. The remaining 18 late cases made up a second group, those from whom diagnostic tissue was obtained after two months or longer.

In early cases, the starch reaction began with abdominal pain (either focal or generalized), tenderness, fever, nausea, and vomiting. A few patients also had diarrhea. Leukocytosis was frequent during the first three weeks and one patient had pronounced eosinophilia. Differential diagnosis included appendicitis, cholecystitis, intra-abdominal abscess, and intestinal obstruction. The latter was the only preoperative diagnosis in 11 symptomatic patients who were operated on more than two months after the initial procedure.

Gross Pathology

At operation, the acute reaction included intraperitoneal fluid, fibrin, and miliary granulomas. Liquid exudate, present in approximately half of the early cases, was often described as pale yellow and turbid; occasionally clear fluid was described. Amounts varied from 30 to 3,000 ml. Fibrinous exudate roughened the inflamed serosal areas, sometimes forming adhesions with adjacent surfaces. Often, the omentum was contracted into a boggy inflammatory mass.

Pale granulomatous nodules were present in nearly all, and were numerous and widespread in most, so that some surgeons erroneously identified the condition as tuberculous peritonitis or, less often, as carcinomatosis.

In the late cases, only scattered firm white nodules and dense fibrous adhesions remained. The miliary nodular structures were present in nine of eighteen of these late cases. Fibrous adhesions producing partial or complete intestinal obstruction were present in 11 of the 18, while adhesions in six others were incidentally observed at autopsy or at operations for unrelated conditions.

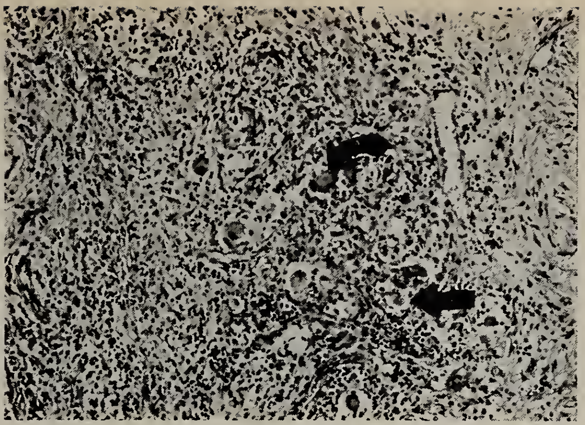

Figure 1.—Nodule from serosa of small intestine, 55 days after hysterectomy and surgical exploration of abdomen. Among the fibroblasts and large capillaries are numerous lymphocytes and phagocytes. Starch granule (straight arrow) and partially disintegrated starch granule (curved arrow) are in foreign body giant cells. (Hematoxylin and eosin, X 160)

Microscopic Pathology

Microscopically, the early lesions consisted of fibrin on the serosa, with fibroblasts and capillaries projecting into the fibrin. This was accompanied by stromal edema and infiltration by polymorphonuclear leukocytes (both neutrophilic and eosinophilic), lymphocytes, and phagocytic cells. Coalescence of phagocytes produced many multinucleated giant cells (Figure 1).

Up to about two months, eosinophils and lymphocytes were numerous, both diffusely and grouped around phagocytic cells. Spherical masses of the latter with central multinucleated giant cells formed many histologic tubercles. Some giant cells contained refractile pale basophilic granules, highly visible as Maltese crosses in the polarized light of Nicol prisms. These starch granules stained readily with iodine or PAS technique. In a few cases, iodine stains were negative while the PAS technique stained material in giant cells that was less sharply defined than typical starch granules. We believe this material is starch which has been partially hydrolyzed, and that it would soon disappear completely.

In late cases, the nodules consisted of necrotic centers surrounded by epithelioid cells in palisade arrangement, each with its dense collagenous envelope. Occasional Langhans giant cells

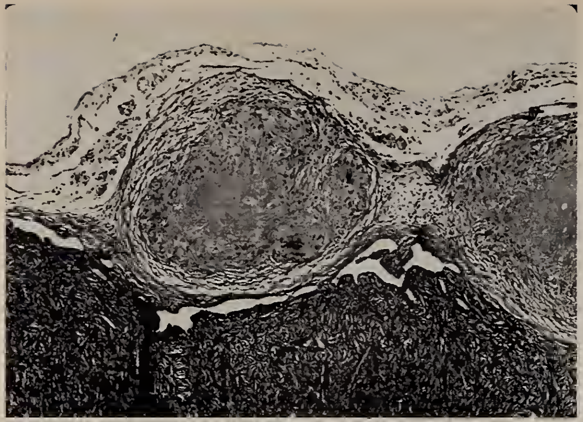

Figure 2.—Two of numerous firm white peritoneal nodules observed at hysterectomy for post menopausal vaginal bleeding five months after cholecystectomy and surgical exploration of abdomen. These were on the surface of a fibrotic ovary. Centers are necrotic and contain PAS-positive starch granules; epithelioid and giant cell zone is surrounded by loose connective tissue containing large capillaries. (Hematoxylin and eosin, X 100)

were in the palisade zone. Scattered granules of starch were within the necrotic material or the palisade layer (Figure 2). Nodular lesions of this type, 1 to 5 mm in diameter, were observed in delicate adhesions which also contained many large capillaries and hemosiderin granules.

Metaplastic mesothelial cells, cuboidal or spherical, were noted in many older cases. In some these cells formed groups between adjacent folds of omentum, and in one case they were so numerous and prominent as to suggest neoplasm.

Not infrequently, in patients who had had surgical operation several years previously, subserosal nodules of dense hyalinized collagen (focally calcified in one case) were found; we believe that these represent the end stage in the evolution of starch granulomas.

Other substances may induce reaction in the peritoneum and must be differentiated from starch. These include talc, gauze lint, suture material, and debris extruded from the digestive tract.[7] Starch may be differentiated from all of these by its fairly uniform size and its reaction with iodine and PAS stains.

Discussion

The necessity of a dry powder lubricant for latex gloves led to the trial of lycopodium spores and later to talc. Within a few years it was recognized that inflammation and adhesions could follow deposition of these substances in the peritoneal cavity. Nevertheless, the use of talc was continued until a substitute lubricating powder, specially refined corn starch,* was described by Lee and Lehman[1] in 1947. Potassium bitartrate[8] was also tested as a replacement for talc, but corn starch was adopted, and within a few years it had replaced talc in the operating rooms of "60 to 90 percent of hospitals in the United States."[2]

Lee and Lehman[1] stated in 1947 that their starch powder "is completely absorbed from the peritoneum without any demonstrated inflammatory reaction," and that "it produces no adhesions whatever." However, subsequent studies by Lee, Collins, and Largen[2] proved that a foreign body reaction does occur during the first three weeks after dispersion of powder into the peritoneal cavity. Clumps of powder prolong the reaction and may lead to fibrosis and adhesions. Lee et al[2] concluded: "Sterilizable corn starch approaches the theoretical ideal as a powder lubricant for gloves. Nevertheless, any powder, no matter how benign it may be or how quickly it is absorbed, produces some degree of foreign body reaction when it contaminates an open wound."

Three years later, in 1955, Sneierson and Woo[9] reported the first complications ascribed to starch powder—two instances of incisional granulomas. Peritoneal reaction in two patients was described the following year[3] and similar cases have been reported singly or in small groups almost every year since. The cases of peritoneal complications up to 1963 were tabulated by Bates,[10] and she added a case of her own.

Between 1964 and 1966, a total of eight cases were the subjects of six papers, and in 1970, two groups of investigators[11,12] described 11 more. Eight of these appeared in a period of six months and were ascribed to a change from corn starch to rice starch by one glove company. The authors[12] believed the rice starch cases to be more severe than the disease caused by corn starch.

It has been impossible to obtain information concerning the origin of the gloves in most of our cases. There is clear evidence that Bio-Sorb is the starch that has been responsible for the majority. We have no information indicating that rice starch was responsible for any of the cases reported here.

The most recent publication[13] on the subject describes the pathologic changes in detail and contributes clinical data on five additional cases of serosal disease caused by starch.

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*Termed "#108," subsequently given the name "Bio-Sorb.®"

Individual idiosyncrasy has been suggested as an explanation of the sporadic occurrence of cases, an idea supported by the occasional case in which there is an eosinophilic leukocyte response. MacQuiddy and Tollmand[14] did skin tests for starch sensitivity on 131 persons, 81 of whom "had allergic backgrounds," without positive results; attempts to elicit sensitivity reactions to parenteral injections in animals were also negative. On the other hand, in the case reported by Bates[10] the patient had abdominal symptoms and a local skin reaction after intradermal injection of an extract of Bio-Sorb. In spite of this unique reaction, we believe that the tissue responses in nearly all cases are probably a direct reaction to the irritating material. The sporadic occurrence of cases may be the result of inadvertent excessive contamination or unusual clumping of the powder granules in these patients. Both experimental and clinical observations prove that these two factors can potentiate reactions, and that fibrous adhesions result from incomplete resolution in such cases.

We have occasionally observed starch granules in adhesions where their role as pathogenic agents would be doubtful. For example, a few particles and granulomas in dense adhesions following operation for a perforated diverticulum of the colon or for pelvic inflammatory disease may be of little or no importance as causative factors. Conversely, starch may not be found in some lesions it has produced; it can completely disappear from the tissues as the inflammation subsides, although fibrosis and adhesions persist.

We have had difficulty in recognizing starch with hematoxylin and eosin stains in some granulomas, while PAS technique or iodine reactions produced unequivocal positive results. Further examination of the hematoxylin and eosin sections revealed finely granular material, presumably partially decomposed starch, instead of the translucent blue granules which characterize fresh starch. This decomposition must occur irregularly, for it is noted in some cases of only a few weeks' duration while typical starch persisted in others for many months.

In early cases, surgical procedures were performed because of the possibility of abscess, appendicitis or intestinal obstruction. In late cases, operation was necessary because of adhesions and intestinal obstruction. Some late lesions were incidental observations at operations for unrelated conditions or at autopsy. Biopsy was the only procedure at most second operations, but in some cases omentectomy and in a few cases cholecystectomy or resection of inflamed segments of intestine was carried out. Some patients who had persistent postoperative pain and fever received postoperative steroid therapy with satisfactory results.

Contamination of surgical specimens by starch is frequent. During microscopic examination of tissue sections, starch granules are often observed at the surfaces, and they may occur throughout the cellular and protein debris of "cell buttons" prepared from abdominal or thoracic fluids. Such contamination of a specimen during or subsequent to the operation at which it was removed should not be erroneously interpreted as a cause of preoperative illness. However, the presence of the granules does direct attention to the fact that starch contamination has not been eliminated, and additional cases of glove starch peritonitis may be anticipated.

In addition to peritoneal lesions, starch granules have been the cause of postoperative granulomas in a variety of wounds leading to abscesses and sinuses. Starch has also caused granulomas of the spermatic cord, paranasal sinuses, mastoid process and middle ear. Contamination of arteriography contrast media with starch granules has led to focal glomerulitis and to petechiae of the skin and retina.

Morbidity from starch peritonitis may be much more widespread than the paucity of reported cases would indicate. With few exceptions each contributing pathologist had more than one case, suggesting that identification of additional cases follows recognition of the entity.

We have also noted that some surgeons and surgical nurses are unaware of the problem, so that precautions to cleanse the gloves of excessive powder are not yet universally observed.

Recognition of the problem and application of appropriate surgical techniques should preclude introduction into wounds of significant amounts of starch. Attention to washing excess powder from the gloves has been advocated for years. However, an affinity seems to exist between starch granules and gloves, since merely withdrawing the hands after rinsing them in the splash basin often leaves the gloves covered with powder granules and aggregates. Presumably this is caused by static electricity, but we find no published study of the phenomenon.

Punctured or torn gloves can yield contamination, including clumps of powder. That this may be a frequent source is suggested by a study some years ago[8] which indicated that 22.6 percent of gloves are perforated during operations, permitting escape of powder from the finger tips.

Other uses of starch powder may lead to its introduction into tissues; rubber drains and tubes have powder on them and unless special efforts are made to remove it, the starch will be introduced into abdominal or other wounds.

Scrupulous cleansing of gloves has been accomplished by wiping them with a moistened cloth after they have been washed in the splash basin. Such cleansing must not be limited to the initial pair of gloves, but to any gloves that are changed during the course of an operation.[15] The effectiveness of these procedures is indicated by Sobel HJ et al,[13] who observed no further cases in a two-year period after these precautions were instituted.

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TENSION HEADACHE TREATMENT WITH ANTIDEPRESSANTS

Ninety percent of all the headaches we see (as general practitioners) are muscle contraction headaches. They are either anxiety or tension or depressive equivalents with conversion reactions. . . .

When you believe that you are dealing with a tension situation, you should do an inventory of the patient—an inventory of his marriage, his occupation, his life stresses, personality traits, habits, and methods of handling tension. Usually by doing a careful inventory you will work out the problems of the patient. Most of the people who come in to see me are not having a simple tension headache. Most of them are depressed. They are usually complaining of a constant daily headache, present all the time. There are certain key questions that we should ask. First, are the headaches relieved by the simple analgesics? They usually are not; aspirin does not relieve them. Then the most important question is about sleep habits. Does the patient have trouble going to sleep? Does he awaken frequently during the night? What time does he get up every morning? Most of these patients will give a history of generalized headache, frequent awakening, and early awakening every morning. You can treat these people with simple antidepressants—the tricyclic antidepressants. I don't care which one you use—amitriptyline, protriptyline, Tofranil®—any one of these will produce good results. You have to give the patient at least a week to ten days of treatment and tell him not to expect results for ten days. He is going to have a dry mouth; he is going to be a little sleepy at first; but after a while he is going to do well.

—SEYMOUR DIAMOND, M.D., Chicago

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Some Potential Interactions Between Prescribed Drugs and Over-the-Counter Drug Products

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MUCH ATTENTION AND PUBLICITY has been given in recent years to the potential interactions between concurrently prescribed prescription drugs. Some interactions are antagonistic; some are synergistic; some are potentially lethal. However, in this context, the over-the-counter (OTC) drugs the patients use (and sometimes abuse) have been relatively ignored.

More medications are available for the relief of coughs and colds than for any other symptom. Hundreds of complex preparations for coughs, colds, hay fever and other respiratory conditions are available in super-markets, cigar stores and motel offices as well as in drug stores.

The ingredients include enzyme inducers (antihistamines), neuromuscular agents (anticholinergics), central nervous system stimulants or depressants, cardiovascular agents (decongestants), nephrotoxic agents (phenacetin) and other potent and toxic pharmacologic categories.

Many of these preparations can be abused by those seeking "kicks" and because they possess the potential for vast numbers of interactions with each other as well as with prescribed medications.

Particular caution should be observed with monoamine oxidase inhibitors (MAOI), tricyclic antidepressants, and other hazardous interactants. Medications for respiratory disorders probably cause more problems than any other single class of therapeutic agents.

There is little, if any, documentation of the many potential interactions between prescribed drugs and OTC drug products. The accumulation of such information is a monumental task as the number of such products is in the thousands, and hundreds more appear every year.

The categories explored herein are internal analgesics, asthma preparations, nasal decongestants, cough and cold remedies, nasal sprays, cough mixtures and sleeping preparations. The tables are limited to the most popular, largest selling brands.

Some sources available to physicians who wish to keep abreast of potential drug interactions are MEDICAL LETTER, CLIN-ALERT, DRUG INTERACTIONS (Hansten, P., Lea & Febiger), HAZARDS OF MEDICATION (Martin, E., Lippincott), and THE HANDBOOK OF DRUG INTERACTIONS (Swidler, G., Wiley-Interscience). For formula and quantities the HANDBOOK OF NON-PRESCRIPTION DRUGS published by the American Pharmaceutical Association lists nearly all OTC products and their formulae that are sold in the United States.

From Palo Alto Medical Clinic, Palo Alto.

Submitted August 17, 1971.

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TABLE 1.—*INTERNAL ANALGESICS: (salicylates as main ingredient)*

A Compound of One of These Products	*(Active Ingredients)*		*When Taken with These Drugs*	*May Cause This Interaction*	*Comment and/or Mechanism of Action*
ASA COMPOUND*	aspirin phenacetin caffeine	227 mg 160 mg 32.5 mg	antidiabetics	hypoglycemia[1]	antidiabetic may be potentiated due displacement of sulfonylureas from protein binding sites.
APC COMPOUND*	aspirin phenacetin caffeine	226 mg 162 mg 32 mg	alcoholic beverages	possible GI bleeding[2]	ethanol appears to increase GI bleeding produced by salicylates; those products containing antihistamines may enhance sedation with ethanol.
ALKA-SELTZER†,**	aspirin calc. phosphate citric acid sod. bicarbonate	325 mg .196 mg 1.055 gm 1.904 gm	anticoagulants	possible bleeding[3,24]	salicylates potentiate effect of anticoagulants; response unpredictable when antihistamines are present. Also potentiated by acetaminophen.
ANACIN*	aspirin caffeine	400 mg 32.5 mg	CORTICOSTEROIDS	steroid effect potentiated[4,5]	increased danger of GIT ulceration. Salicylates and corticosteroids are both ulcerogenic.
ANACIN ARTHRITIS FORMULA**	aspirin alum. hydroxide[a] mag. hydroxide[a]	500 mg	diphenylhydantoin	potentiation of diphenylhydantoin[6]	large doses of salicylates enhance effect; an effect of salicylates on renal excretion may be involved.
ASCRIPTIN**	aspirin alum. & mag. hydroxide[a]	300 mg	hypotensives	reversal of hypotensive	caffeine present may in sufficient doses stimulate rise in pressure.
BUFFERIN**	aspirin alum. dihydroxyaminoacetate, 49 mg. mag. carb. 97 mg	324 mg	methotrexate	pancytopenia[3]	methotrexate may be displaced from albumin binding site resulting in increased toxicity.
BROMO SELTZER†,**,§	pot. bromide sod. bicarb. & citric ac.[a]	162.5 mg	oxyphenbutazone	diminished oxyphenbutazone effect[7]	evidence indicated salicylates and uricosuric agents share a common binding site on plasma albumin molecule. Also increased danger of gastrointestinal tract ulceration.
CAMA**	aspirin mag. hydroxide alum. hydroxide	600 mg 150 mg 150 mg	p-aminosalicylic acid	salicylism[8]	possibly due to increased PAS toxicity.
COPE*,**,††	aspirin caffeine methapyrilene alum. hydroxide mag. hydroxide	420 mg 32 mg 15 mg 25 mg 50 mg	phenobarbital	diminished effect of salicylates[9]	diminished effect due to enzyme induction by phenobarbital.
DOAN'S PILLS	THEOBROMINE sod. salicyl.[a] Ext. Uva Ursi,[a] Ext. Buchu,[a] Vitamin A[a]		phenylbutazone	possible GI bleeding; water retention[7,10]	phenylbutazone inhibits the uricosuria that follows large doses of salicylates. Also may increase danger of GIT ulceration. Both drugs are ulcerogenic.
ECOTRIN	aspirin (enteric coated)	300 mg	PREDNISONE	salicylism[4,15]	rise in blood salicylate levels when prednisone is discontinued.

EMPIRIN COMPOUND*	aspirin phenacetin caffeine	233 mg 166 mg 30 mg	probenecid	probenecid effect blocked[3]	uricosuric action blocked by salicylates in analgesic doses; salicylates and uricosuric agents may share a common binding site on plasma albumin molecule.
EXCEDRIN*	aspirin caffeine salicylamide acetominophen	190 mg 60 mg 130 mg 90 mg	sulfinpyrazone	sulfinpyrazone effect diminished[7,10]	analgesic doses of salicylates may antagonize uricosuric effect.
FIZRIN†,**	aspirin[a] citric acid[a] sod. bicarbonate[a]		tricyclic antidepressants	potentiated[25]	alkalinizing agents such as pot. cit. or sod. bicarb. may decrease urinary excretion; concomitant administration with antihistamines may produce atropinism (hazardous in glaucoma) by additive effect.
MEASURIN	aspirin (time release)	660 mg			
MIDOL*	aspirin caffeine cinnamyl ephedrine	450 mg 32 mg 15 mg			
PAMPRIN††	phenacetin salicylamide pamabron pyralimine maleate	125 mg 125 mg 25 mg 25 mg			
PERCOGESIC††	acetaminophen phenyltoloxamine cit.	325 mg 30 mg			
VANQUISH*,**	aspirin caffeine acetaminophen alum. hydroxide mag. hydroxide	227 mg 33 mg 194 mg 25 mg 50 mg			
ZUMARIN	salicylamide potass. salicylate	226 mg 230 mg			

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*Caffeine may cause excitation response with MAOI; may reverse hypotensive drugs

†Excess dosage may cause alkalosis, basic urine; amphetamine activity enhanced in basic urine due to decreased rate of excretion[30]

**May chelate or otherwise interfere with absorption of tetracyclines

††See Table 6 (antihistamines)

§Bromides taken with phenacetin over long periods may cause cyanosis; bromide intoxication associated with sulphaemoglobinemia; the major hazard of phenacetin abuse is renal damage.[29]

[a] Quantitative amounts not supplied

TABLE 2.—*INHALATION PRODUCTS: (epinephrine as main ingredient)*

Any of These Products	*(Active Ingredients)*		*When Taken with These Drugs*	*May Cause This Interaction*	*Comment and/or Mechanism of Action*
ADRENALIN	epinephrine HCl	1%	furazolidone (after days of therapy acts as MAOI)	hypertension, excitation[11,12]	metabolism of norepinephrine is inhibited at storage sites, building up high blood-brain levels
ASTHMANEFRIN	epinephrine HCl (racemic)	.83%			
BREATHEASY	epinephrine HCl* (racemic)		MAOI	as above	as above
			Digitalis glycosides	Cardiac arrhythmia[13,25]	adrenergic drugs such as ephedrine and epinephrine may predispose patient to cardiac arrhythmias
BRONKAID MIST	epinephrine HCl	.5%			
MEDIHALER-EPI	epinephrine bitart	.7%	hypotensive drugs	hypertension	reversal of effect of hypotensive agent possible through over-use
PRIMATENE MIST	epinephrine HCl	.5%			
VAPONEFRIN	epinephrine HCl (racemic)	2.25%	procarbazine (acts as MAOI)	hypertension, excitation[11,12]	metabolism of norepinephrine is inhibited at storage sites, building up high blood-brain levels
			insulin and oral antidiabetics	hyperglycemia[14]	epinephrine may raise blood sugar levels by stimulating release of glycogen
			sympathomimetics	status asthmaticus[15]	potentially lethal
			tricyclic antidepressants	enhanced adrenergic effects[20,27]	response unpredictable

TABLE 3.—*LIQUID DECONGESTANTS, COUGH SUPPRESSANTS: (antihistamines and sympathomimetics as main ingredient)*

Any of These Products	*(Active Ingredients)*		*When Taken with These Drugs*	*May Cause This Interaction*	*Comment and/or Mechanism of Action*
CHERACOL D*†§	dextromethorphan (per oz.) glyceryl guaiacolate amon. chlor.	60 mg 71 mg 518 mg	alcoholic beverage	CNS depression[10,23]	enhanced sedation, additive effects: large amounts of alcohol may cause hypertension (potentiates adrenergic effects of sympathomimetics) (except Cheracol D)
COLDENE††§	phenylpropanolamine d-methorphan chlorpheniramine	11 mg 7.5 mg 1 mg	anticoagulants	may decrease anticoagulant effect[17,24]	antihistamines may cause reversal of anticoagulant effect by enzyme induction; acetaminophen may potentiate; response unpredictable

NOVAHISTINE††	phenylephrine chlorpheniramine	10 mg 2 mg
NOVAHISTINE-DH††	same as above plus codeine phos.	 10 mg
NYQUIL**§	acetominophen ephed. sulf.[a] doxylamine[a] d-methorphan[a] alcohol	.6 gm/oz 25%
SUPER ANAHIST SYR.§	thonzylamine ammon. chlor. d-methorphan	12.5 mg 100 mg 10 mg
TRIAMINIC††	phenylpropanolamine pheniramine mal. pyrilamine mal. glyceryl guaiacolate	12.5 mg 6.25 mg 6.25 mg 100 mg
TRIAMINICOL††§	same as above plus d-methorphan	 15 mg
TRIND††	phenylephrine HCl glyc. guaiacol. acetominophen	2.5 mg 50 mg 150 mg
VICK'S FORMULA 44§	d-methorphan[a] doxylamine succ.[a]	

anticholinergics	atropinism, excessive dryness[8,18,22]	anticholinergics and antihistamines may have additive effects since many antihistamines have anticholinergic properties. Combination is hazardous because of enhanced mydriasis
barbiturates	CNS depression[5,19]	additive effects of barbiturates with antihistamines: with continued use, may lead to mutual inhibition and possible barbiturate tolerance and habituation
DOXEPIN	sedation, atropinism[3]	may enhance effect of antihistamine due to additive effects
MAOI (see note § below re Nardil) [phenelzine]	sedation, atropinism[20,24]	may enhance effect of antihistamine due to enzyme inhibition. Severe hypertension is possible due to presence of phenylephrine and/or phenylpropanolamine
narcotics	sedation[3]	enhanced antihistamine-narcotic synergistic activity
reserpine	CNS depression[5]	antihistamines plus reserpine-synergistic effect: sympathomimetic may antagonize hypotensive effect
sedatives and hypnotics	CNS depression[5]	sedative effect may be initially enhanced
steroids	decreased steroid effect[3,8]	rapidly metabolized due to enzyme induction
tranquilizers	CNS depression, atropinism (especially with phenothiazine[3]	additive sedative effects between antihistamines and tranquilizers: hypotensive effect of phenothiazines may be counteracted by pressor amines
tricyclic antidepressants	potentiation[26]	sympathomimetic and tricyclic may be mutually potentiated

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[a] Quantitative amounts not supplied

*Metabolic acidosis may result from overdosage

†Contains neither antihistamine nor sympathomimetic

**Note: recommended dosage of NYQUIL is 30 cc, equivalent of 30 cc 50 proof alcoholic beverage

††See Table 2, sympathomimetics

§Nardil (phenelzine) potentially lethal with d-methorphan[28]

TABLE 4.—*NASAL DECONGESTANTS: (antihistamines and sympathomimetics as main ingredients)*

Any of These Products	*(Active Ingredients)*	
ALLEREST*	phenylpropanolamine HCl	50 mg
	pyralamine mal.	15 mg
	methapyrilene fumar.	10 mg
CONTAC**	phenylpropanolamine HCl	50 mg
	chlorpheniramine mal.	4 mg
	belladonna alkaloids	.2 mg
CORICIDIN*	chlorpheniramine mal.	2 mg
	aspirin	390 mg
	caffeine	30 mg
CORICIDIN-D*	same as Coricidin plus	
	phenylephrine HCl	10 mg
CORICIDIN *DEMILETS**	phenylephrine HCl	2.5 mg
	chlorpheniramine	0.5 mg
	aspirin	80 mg
CORICIDIN *MEDILETS**	chlorpheniramine	5 mg
	aspirin	80 mg
DRISTAN*†	phenylephrine HCl	5 mg
	phenindamine tart.	10 mg
	aspirin,[a] caffeine,[a] alum. hydrox.,[a] mag. carb.[a]	
ORNEX*	phenylpropanolamine	18 mg
	acetaminophen	175 mg
	salicylamide	150 mg
	caffeine	15 mg
SINUTABS	phenylpropanolamine	25 mg
	phenyltoloxamine cit.	22 mg
	phenacetin	150 mg
	acetaminophen	150 mg
SUPER ANAHIST*	phenylpropanolamine	25 mg
	phenyltoloxamine cit.	6.25 mg
	thonzonium HCl	6.25 mg
	phenacetin	97.2 mg
	aspirin	227 mg
	caffeine,[a] ascorbic acid[a]	

When Taken with These Drugs	*May Cause This Interaction*	*Comment and/or Mechanism of Action*
alcoholic beverages	CNS depression[16,23]	enhanced sedation effect between alcohol and antihistamines; large amounts of alcohol potentiates adrenergic effects of sympathomimetics
anticoagulants	diminished effect of anticoagulant[17,24]	antihistamines may cause reversal of anticoagulant effect; acetaminophen may potentiate; response unpredictable
anticholinergics	atropinism[8,18,22]	anticholinergics and antihistamines may have additive activity; many antihistamines have anticholinergic effects; combination may be hazardous because of enhanced mydriasis
antidiabetics	hyperglycemia[14]	sympathomimetics may raise blood level of sugar by stimulating release of glycogen
barbiturates	sedation[5,19]	antihistamines and barbiturates may have additive effects; with continued use may lead to mutual inhibition and possible barbiturate tolerance and habituation
doxepin	CNS depression,[3] atropinism	enhanced sedation due to effect of doxepin with antihistamine; both have anticholinergic effects
hypotensives	hypertension	reversal of hypotensive effect by sympathomimetic
MAOI drugs	sedation, atropinism, hypertension[20,21]	hypertensive crisis may also occur due to inhibition of metabolism of sympathomimetics, especially phenlyephrine
levodopa	hypertension[3]	levodopa may inhibit metabolism of sympathomimetics
narcotics	sedation[3]	enhanced sedation by antihistamine; potentiated by narcotic's depressant action
procarbazine	CNS depression, atropinism[20,21]	procarbazine acts as MAOI; hypertension may result when administered with sympathomimetic

TRIAMINICIN*†	phenylpropanolamine pheniramine mal. pyrilamine mal. aspirin acetaminophen caffeine ascorbic ac. al. hydrox. gel (dried)	25 mg 12.5 mg 12.5 mg 225 mg 150 mg 30 mg 50 mg 180 mg	reserpine	CNS depression,[5] atropinism	synergistic depressant effect between reserpine and antihistamine: sympathomimetic may antagonize hypotensive effect
			sedatives and hypnotics	CNS depression[5]	sedative effect may be initially enhanced
			steroid hormones	decreased hormone[3,8] effect	due to enzyme induction, rapidly metabolized
URSINUS*	phenylpropanolamine pheniramine mal. pyrilamine mal. aspirin (equiv.)	25 mg 12.5 mg 12.5 mg 300 mg	tranquilizers	CNS depression[3] (especially with phenothiazines)	additive with antihistamines: hypotensive effect of phenothiazines may be counteracted by pressor amines
			tricyclic antidepressant	potentiation[26]	sympathomimetic and tricyclic may be mutually potentiated

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[a] Quantitative amounts not supplied
*Plus salicylates
†May chelate tetracyclines (alum., cal., magn. ions)
**Belladonna contra-indicated in glaucoma

TABLE 5.—*NASAL DECONGESTANTS (DROPS AND SPRAYS): #(antihistamines and/or sympathomimetics as main ingredients)*

Any of These Products	*(Active Ingredients)*		*When Taken with Any of These Drugs*	*May Cause This Interaction*	*Comment and/or Mechanism of Action*
ALCONEFRIN	phenylephrine (asst. strengths)		anticoagulants (with antihistamine containing drugs)	reversal of anti-anticoagulant[17,24]	over-use may decrease effect of anticoagulant (antihistamine content)
CONTAC SPRAY	phenylephrine methapyrilene	0.5% 0.2%	digitalis	arrhythmias[13,25]	ephedrine and eprinephrine combined with digitalis glycosides predispose patient to cardiac arrhythmias
CORICIDIN MIST	phenylephrine methapyrilene	0.5% 0.3%			
NTZ	phenylephrine thenfadil	0.25% 0.1%	furazolidone and MAO inhibitors, also procarbazine	hypertension, excitation[3]	due to possible inhibition of metabolism of sympathomimetic
NEO SYNEPHRINE	phenylephrine (asst. strengths)		insulin and oral antidiabetic drugs	hyperglycemia[14]	sympathomimetic may cause rise in blood sugar by stimulating release from liver of glycogen
PRIVINE	naphazoline	0.5%			
SINEX	phenylephrine[a] methapyrilene[a]		L-dopa	mydriatic effect of phenylephrine reduced possible hypertension[3]	competitive a-adrenergic receptor blockade
DRISTAN	phenylephrine[a] pheniramine[a]		phenothiazines	hypertension[3]	phenylephrine antagonizes hypotensive effect of phenothiazines
VICK VATRONOL+	ephedrine sulf.[a] methapyrilene[a]		tricyclic antidepressants	potentiation[26]	sympathomimetic and tricyclic may be mutually potentiated

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#This class of products is notorious for over-use, therefore included
[a] Quantitative amounts not given
+Digitalis glycosides with ephedrine and related adrenergics may cause cardiac arrhythmias when over-used

TABLE 6.—*SLEEPING AIDS: (antihistamines as main ingredient)*

Any of These Products	*(Active Ingredients)*		*When Taken with Any of These Drugs*	*May Cause This Interaction*	*Comment and/or Mechanism of Action*
DORMIN	methapyrilene	25 mg	alcoholic beverage	CNS depression[10,23]	enhanced sedation due to synergistic activity of antihistamine with alcohol
NYTOL	methapyrilene	25 mg			
	salicylamide	200 mg	anticholinergics	atropinism[8,22]	antihistamines also have an anticholinergic effect
SLEEP EZE*	methapyrilene	25 mg			
	scopolamine	0.125 mg	anticoagulant	decreased anticoagulant effect[17]	decreased by concomitant antihistamines
SOMINEX*	methapyrilene	25 mg			
	scopolamine	0.25 mg	barbiturates, sedatives, hypnotics, also reserpine	CNS depression[5,10]	barbiturate potentiated by antihistamines; may increase depth and duration of barbiturate narcosis
	salicylamide	200 mg			
			doxepin	sedation, atropinism[3]	additive effect
			narcotics	CNS depression[3]	enhanced sedation by antihistamine
			MAOI	sedation, atropinism[20,21]	due to inhibition of metabolism
			steroid hormones	decreased steroid effect[3,8]	due to enzyme induction
			tricyclic antidepressants	atropinism[25]	concomitant administration with antihistamines may produce atropinism (hazardous in glaucoma) by additive effect.

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*Contraindicated in glaucoma, asthma, hepatitis, and toxemia of pregnancy because of scopolamine content (salicylates not considered in this table. See Table 1.)

TRADE AND GENERIC NAMES OF PRESCRIPTION DRUGS REFERRED TO IN TABLES

Dialog,® Tylenol,® Trind®	acetaminophen
Dilantin®	diphenylhydantoin
Sinequon®	doxepin
Furoxone®	furazolidone
Larodopa,® Dopar®	*levodopa*
Eutonyl,® Nardil,® Marplan,® Parnate,® Niamid,® Matulane®	MAOI
Tandearil®	oxyphenbutazone
Compazine,® Mellaril,® Thorazine,® Phenergan,® Sparine,® Stelazine®	phenothiazines
Butazolidin,® Butazolidin Alka®	phenylbutazone
Benemid®	probenecid
Matulane®	procarbazine
Serpasil,® Sandril®	reserpine
Equanil,® Miltown,® (and meprobamate compounds), *Librium,® Valium,® Serax,®* chloral hydrate, *Quaalude,® Parest,® Dalmane®*	sedatives, hypnotics
Anturane®	sulfinpyrazone
Aventyl,® Elavil,® Norpramin,® Pertofrane,® Tofranil,® Triavil,® Vivactil,® Etrafon®	*tricyclic antidepressant*

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STRAIGHT EYES OR BINOCULAR VISION—WHICH?

True or False: The restoration of single binocular vision in the patient with strabismus is the ultimate goal of all therapy.

False. I would like to go on record . . . saying that I think the cosmetic result is more important. It's the most important result for the parent, for the child, and ultimately for the ophthalmologist as well. However, I think we should strive to obtain binocular vision, too, because those patients who have singular binocular vision have the best-looking pair of eyes. Interestingly enough a number of years ago this concept was brought out in a big strabismus meeting in France. The French ophthalmologists who said that the cosmetic appearance was most important were butchered by the English and American ophthalmologists who said that binocularity was the most important thing. As long as there is nobody else around but ophthalmologists, let's admit that the cosmetic result is the most important.

—EUGENE R. FOLK, M.D., Chicago
Extracted from *Audio-Digest Ophthalmology,* Vol. 9, No. 15, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

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Prescription Data Processing— Its Role in the Control of Drug Abuse

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■ *Prescriptions in an outpatient setting were kept on file for immediate recall by computer terminals. Drugs with abuse potential were found to make up 33.6 percent of all prescriptions, and 12.4 percent of these prescriptions were for excessive quantities. An additional 2.6 percent of these prescriptions represented irrationally large quantities of drugs dispensed by multiple prescriptions. The physician was cooperative and willing to correct this situation when it was brought to his attention by the pharmacist.*

IN THE YEAR 1970, MORE than 7,000 patients were admitted to the Los Angeles County-University of Southern California Medical Center because of serious and sometimes fatal drug abuse. They accounted for roughly 20 percent of all admissions to the medical wards.

Some of these patients were suffering from alcoholic intoxication or alcohol withdrawal. Others, including many young persons, had taken heroin, LSD or other illegal drugs. In the majority of patients, however, care in hospital was required because of the misuse or abuse of medicinal agents legally on the market. (Not included here are those who required admittance to hospital because of such adverse drug reactions as allergic responses.)

The results of this misuse or abuse of prescription drugs, whether accidental or deliberately intended, pose a particular challenge to physicians, pharmacists and other health professionals. Although it seems likely that some of the prescription products implicated in these cases may have been obtained through the black market or other illicit channels, it is evident that a substantial proportion was legally prescribed by a physician and legally dispensed by a pharmacist.

An opportunity to conduct long-needed studies in this field has been provided at the Medical Center, where a drug utilization review program was begun in 1967 as part of an effort to examine and improve the prescribing patterns of physicians. From this hospital, one of the largest in the world, more than 600,000 outpatient prescriptions are dispensed each year. Nearly all are obtained at little or no cost by patients who are indigents or beneficiaries of a welfare program. At the core of the program is an electronic data processing (EDP) system, with its appropriate computer terminals, that simultaneously stores the prescription information in a data bank and prints the label in the dispensing pharmacy. Details of the operation are described elsewhere.[1,2]

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Use of the computer system has already made it possible to analyze three types of undesirable or inappropriate prescriptions — (a) excessive quantities specified in an individual prescription, (b) undesirably frequent prescriptions for the same drug, and (c) inappropriate concurrent prescriptions for different drugs. A previous investigation has indicated that more than 12 percent of all outpatient prescriptions dispensed at the Medical Center may be judged to be irrational on these grounds alone.[3]

It has now become evident that the EDP system may also provide some insight into some aspects of drug abuse and the problem of the so-called "prescription shopper"—the patient who obtains two or more prescriptions for the same drug, from either the same or different physicians, at remarkably frequent intervals.

TABLE 1.*—*Defined Limits (Capsules or Tablets) for Excessive-Quantity Single Prescriptions of "Dangerous" Drugs, and for Multiple Prescriptions Involving Excessive Amount in Possession*

Drugs and Dosage	*Single Rx*	*Multiple Rxs*
Amobarbital—30, 60, 100, 200 mg	60	75
Chloral Hydrate—500 mg	100	150
Chlordiazepoxide—5, 10, 25 mg	100	150
Diazepam—2, 5, 10 mg	100	150
Hydroxyzine—25, 50 mg	100	150
Mephobarbital—32, 200 mg	300	450
Meprobamate—400 mg	100	150
Methylphenidate—5, 10, 20 mg	120	180
Phenobarbital—15, 30, 60 mg	200	250
Pentobarbital—30, 100 mg	60	75
Propoxyphene—32, 65 mg	100	150
Secobarbital—30, 100 mg	60	75

*amphetamines are no longer included in our formulary

Preliminary Survey

In 1970, a preliminary analysis during one month revealed that many thousands of outpatient prescriptions had been dispensed for a number of products considered to possess a serious potential for abuse. Some of these represented single prescriptions calling for excessive quantities, but many involved two or more prescriptions together calling for excessive quantities theoretically in the possession of the patient.

Most frequently involved were such tranquilizers and sedatives as diazepam (Valium®), chlordiazepoxide (Librium®), phenobarbital, secobarbital (Seconal®), meprobamate (Miltown,® Equanil®) and chloral hydrate, and one analgesic propoxyphene (Darvon®).

Typical of the recipients of multiple prescriptions was one woman who obtained six prescriptions totaling 645 capsules of propoxyphene 65 mg, dispensed April 2, 3, 7, 23, 26 and 30. Three of these—including the prescriptions written on April 2 and 3—were ordered by the identical physician.

Another patient obtained five prescriptions totaling 480 tablets of meprobamate 400 mg, on April 6, 10, 10, 17, and 23. The five prescriptions were written by five different physicians.

In this preliminary study, 59 cases appeared to represent clear instances of drug abuse. In 28 of these, the patients obtained the multiple prescriptions for the same drug from different physicians in different clinics. One of the patients died. This patient received 400 65-mg capsules of propoxyphene within a seven-day period. The autopsy report from the Coroner's office of Los Angeles County indicated a toxic and presumably fatal concentration of propoxyphene in the tissues. Another group of 20 patients obtained multiple prescriptions from the same clinic, and in 13 of these cases the multiple prescriptions were written by the same physician.

A third group included 11 patients who received two prescriptions for the same drug within a 24-hour period. In one case, according to the chart, the patient claimed that his first prescription had been stolen from him. In another, a failure in the EDP system was apparently responsible. In the remaining nine, no explanation was entered on the chart to indicate the need for the second prescription.

The 1971 Study

On the basis of the 1970 survey, a more searching investigation was conducted during the months of April, May and June, 1971. The study was focused on various dosage strengths of 12 "dangerous" drugs. These substances, together with the maximum number of units arbitrarily defined as safe for a single prescription and the maximum number defined as safe for a patient to have in his possession at one time, are shown in Table 1. (In some instances, these maximum limits differ from those listed in earlier publications.)

The drugs were selected by a committee of physicians at the Medical Center in consultation

TABLE 2.—*Summary of Excessive-Quantity Single and Multiple Prescriptions For "Dangerous" Drugs—April, May and June 1971*

Month	*Total No. "Dangerous" Drug Rxs*	*Excessive Quantity Single Rxs* *No.*	*%*	*Rxs Involved in Excessive Amount in Possession* *No.*	*%*	*Totals** *No.*	*%*
April	8,024	983	12.25	232	2.89	1,142	14.23
May	9,849	1,141	11.58	249	2.53	1,322	13.42
June	8,729	1,163	13.32	212	2.43	1,295	14.84
Total	26,602	3,287	12.36	693	2.61	3,759	14.13

*Some excessive-quantity single prescriptions also included in those involved in excessive amount in possession.

TABLE 3.—*Summary of Excessive-Quantity Single Prescriptions for the Drugs That Comprised 92 Percent of All Prescriptions for "Dangerous" Drugs*

Drug	*April* *No. of Rxs*	*(% total in excess)*	*May* *No. of Rxs*	*(% total in excess)*	*June* *No. of Rxs*	*(% total in excess)*
Propoxyphene	133	(13.6)	125	(10.9)	149	(12.8)
Diazepam	391	(39.9)	425	(36.3)	444	(38.4)
Chlordiazepoxide	289	(29.5)	329	(28.8)	312	(26.8)
Phenobarbital	92	(9.4)	157	(13.7)	140	(12.0)

with members of the psychiatric staff who have had considerable experience with drug abuse problems. The 12 "dangerous" drugs listed here were defined by the group as having grave potential for abuse, and have been observed to be employed most frequently by drug abuse patients. The amounts of these agents used by drug abusers are generally far in excess of the normally recommended therapeutic doses. When these drugs are obtained by legal prescription, it is common for the prescription shopper to seek multiple prescriptions from multiple sources within a relatively brief time span.

During the three-month period of study, 26,602 prescriptions were dispensed for these agents, accounting for 23.3 percent of all prescriptions. Of these, 3,287, representing 12.36 percent of all "dangerous" drug prescriptions, involved single prescriptions calling for quantities exceeding the defined safe limit, while 693, or 2.61 percent (including some single orders for excessive quantities) were involved in irrational multiple prescriptions. Of all prescriptions for these 12 "dangerous" drugs, 3,759 or 14.13 percent were therefore involved in excessive prescribing. This situation is summarized in Table 2.

Excessive-Quantity Single Prescriptions

An analysis of the prescriptions containing quantities above the defined limits of safety indicated that the drugs most frequently involved were diazepam, chlordiazepoxide, phenobarbital and propoxyphene. These four accounted for about 90 percent of all excessive-quantity prescriptions. It appears noteworthy that most of the excessive-quantity prescriptions for diazepam and chlordiazepoxide were generated from the general medical clinics, while few came from the psychiatric service. Table 3 summarizes these data.

In some instances, single prescriptions called for quantities far above the defined limits of safety—as many as 500 capsules of propoxyphene, 800 capsules of chlordiazepoxide, 600 tablets of diazepam, 500 tablets of meprobamate, and 1,000 tablets of phenobarbital.

Multiple Prescriptions

The nature of irrational multiple prescriptions for the same drug may be illustrated by the hypothetical case of a patient who is given 90 capsules of chlordiazepoxide 10 mg—equivalent to a 30-day supply—and then, two days later, is given an additional 90 capsules of the same drug by either the same or a different physician. Neither prescription would exceed the defined limit of 100 units for a single prescription, but the two prescriptions together would provide an unacceptable quantity in the possession of the patient.

An analysis of such multiple prescriptions dis-

TABLE 4.—*Multiple Rxs for "Dangerous" Drugs Involved in Excessive Amount in Possession*

Drug	*April* No. of Rxs	(% total)	*May* No. of Rxs	(% total)	*June* No. of Rxs	(% total)
Diazepam	85	(36.6)	83	(33.3)	68	(32.0)
Chlordiazepoxide	58	(25.0)	53	(21.2)	38	(17.9)
Propoxyphene	52	(22.4)	43	(17.2)	55	(25.9)
Phenobarbital	18	(7.7)	36	(14.4)	18	(8.4)
Subtotal	213	(91.7)	215	(86.1)	179	(84.2)
Others	19	(8.3)	34	(13.9)	33	(15.8)
Total	232	(100.0)	249	(100.0)	212	(100.0)

TABLE 5.—*Number of Patients with Excessive Quantities of "Dangerous" Prescription Drugs in Possession*

Drug	*April*	*May*	*June*	*Total*
Amobarbital	0	0	1	1
Chloral Hydrate	3	5	2	10
Phenobarbital	9	16	9	34
Secobarbital	1	6	9	16
Diazepam	38	36	36	110
Meprobamate	4	3	2	9
Pentobarbital	1	1	0	2
Propoxyphene	21	18	20	59
Chlordiazepoxide	27	24	18	69
Mephobarbital	0	1	1	2
Hydroxyzine	0	0	0	0
Methylphenidate	0	0	0	0
Totals	104	110	98	312

pensed during the study period is given in Table 4. Again the drugs most frequently involved were diazepam, chlordiazepoxide, propoxyphene, and phenobarbital. The number of patients involved in these irrational multiple prescriptions is shown for each month in Table 5. The number of these patients—an average of slightly more than 100 per month—is not large, but each may represent a serious or perhaps fatal clinical problem. Among these patients are almost certainly a considerable number of prescription shoppers.

The problem of multiple prescriptions may be illustrated by such cases as the following (in these records, the numbers of days' supply have been derived from the prescription directions):

Patient A.—six prescriptions for meprobamate from six physicians—150 tablets (50 days) on April 4, 100 tablets (25 days) on April 20, 100 tablets (33 days) on May 4, 100 tablets (33 days) on May 14, 400 tablets (33 days) on June 8, and 100 tablets (34 days) on June 22.
(950 tablets dispensed in 78 days.)

Patient B.—two prescriptions for diazepam, each for 200 tablets (50 days) from two different physicians on the same day.
(400 tablets dispensed in one day.)

Patient C.—three prescriptions for diazepam from the same physician—100 tablets (25 days) on April 12, 100 tablets (25 days) on April 26, and 100 tablets (25 days) on April 28.
(300 tablets dispensed in 17 days.)

Patient D.—two prescriptions for diazepam from two physicians in different clinics, each for 300 tablets (150 days), on the same day.
(600 tablets dispensed on one day.)

Patient E.—two prescriptions for chlordiazepoxide from the same physician—200 capsules (66 days) on April 8 and 200 capsules (50 days) on April 12.
(400 capsules dispensed in five days.)

Patient F.—ten prescriptions for propoxyphene from seven different physicians—100 capsules (16 days) on April 6, 100 capsules (16 days) on April 13, 100 capsules (16 days) on April 20, 300 capsules (75 days) on April 22, 100 capsules (16 days) on April 22, 50 capsules (9 days) on June 2, 100 capsules (17 days) on June 3, 60 capsules (10 days) on June 7, 36 capsules (6 days) on June 24, and 100 capsules (9 days) on June 29. The three prescriptions dispensed on April 20 and April 22 were written by the same physician.
(1,046 capsules dispensed in 85 days, and 700 of these in 17 days.)

Patient G.—three prescriptions for mephobarbital from three physicians—100 tablets (25 days) on June 5, 600 tablets (50 days) on June 8, and 400 tablets (100 days) on June 22.
(1,100 tablets dispensed in 18 days.)

Patient H.—two prescriptions for phenobarbital from two different physicians in the same clinic, one for 300 tablets (150 days) and the

other for 500 tablets (167 days), both dispensed on the same day.
(800 tablets dispensed in one day.)

One physician wrote two prescriptions for phenobarbital for *Patient J*, each for 400 tablets (200 days) on May 17 and May 18, respectively. *(800 tablets dispensed in two days.)* The same physician wrote two prescriptions for phenobarbital for *Patient K*, each for 150 tablets (50 days) on May 18 and May 19, respectively. *(300 tablets dispensed in two days.)* He also wrote two prescriptions for phenobarbital for *Patient M*, each for 400 tablets (200 days) on May 26 and May 27, respectively. *(800 tablets dispensed in two days.)*

Patient N.—received two prescriptions for diazepam—100 tablets (25 days) on May 21, and 60 tablets (15 days) on May 23. She received two prescriptions for phenobarbital —100 tablets (33 days) on May 21 and 300 tablets (50 days) on May 23. She also received two prescriptions for propoxyphene—100 capsules (16 days) on May 21 and 100 capsules (16 days) on May 23. All six prescriptions were written by the same physician.

During the study, it was found that two prescriptions for the same drug, written by the same or different physicians, were dispensed within a period of 24 hours in the case of 50 patients. In many of these instances, with patients moving from one clinic to another sometimes within a few hours, it was observed that the second physician did not have the patient's chart available to him for review.

Control Approaches

In order to minimize the types of irrational prescribing described above, three possible approaches were considered.

1. The *patient* might be educated or induced to seek or accept only those prescriptions that did not exceed defined quantity limits.

No practical means to utilize this approach were obvious.

2. The *physician* might be induced to limit his prescribed quantities to those below the defined quantity limits.

As observed earlier,[3] approximately 50 percent of all inappropriate prescriptions were written by less than 4 percent of all prescribing physicians on the Medical Center staff. Personal discussions with this very small percentage of prescribers resulted in a modest but inadequate change in their prescribing patterns.

3. The *pharmacist* might be utilized as the key person in detecting apparently inappropriate prescriptions and initiating corrective steps.

Since June 1971, this approach has been utilized on an experimental basis, taking advantage of the capability of the computer-based electronic data processing system to retrieve and display on a cathode ray terminal screen patient drug data in a few seconds.

In one of the two Medical Center pharmacies dispensing outpatient prescriptions, pharmacists and phramacist technicians were trained to intercept prescriptions calling for certain "dangerous" drugs, particularly those calling for the products listed in Table 1. Under this system, a pharmacist or technician receiving a potentially irrational prescription could take one of two steps:

—If given a prescription calling for an excessive quantity of a "dangerous" drug, he could consult immediately with the prescribing physician before typing the label and processing the prescription.

—If given a prescription calling for an apparently appropriate quantity of a "dangerous" drug, he could obtain a virtually instant display of the patient's drug record on the screen of his terminal, and then—if it seemed necessary—consult with the physician before proceeding to process the prescription.

In some instances, the patient's record has shown that filling the new prescription would not provide him with excessive quantities of the drug in his possession. In others, however, it has been obvious that filling a new prescription—although it in itself was under the defined limits for a single prescription—would give the patient an excessive quantity.

In one case, for example, the record search showed that a patient had received a 50-day supply of diazepam on June 1 and had been given a prescription for a new supply on June 20. Here a consultation with the physician was indicated, and the second prescription was cancelled.

In another, the record search revealed that one patient presenting a prescription on June 15 for 15 tablets of secobarbital 100 mg (a 15-day supply) had obtained 100 tablets on May 7, 20 tablets on May 9, 100 tablets from one doctor and another 50 tablets from a different doctor on May 28, and 100 tablets on June 4. Again, a consultation was clearly indicated, and the physician agreed to alter his treatment schedule.

A survey of 106 such cases demonstrated that in 44 instances the physician ordered the prescription cancelled, in 16 he reduced the prescribed quantity, in 2 he ordered a different drug, and in 38 he approved dispensing the drug as prescribed.

Among the reasons given for approving the apparently irrational prescriptions were these—

"She needs them."

"The daily dosage has been increased."

"Fill this one, but have the patient come back and see me."

"This 91-year-old man has severe Parkinsonism. So has his 85-year-old wife. This one prescription is for both of them. In the future, I'll write two separate prescriptions."

"She's a big woman. She needs the full prescription."

None of the physicians involved in these cases expressed any resentment, and most offered their thanks to the pharmacist. Several indicated they were unaware that the patient had been under concurrent treatment by another physician.

For those patients whose responses to cancellation of a prescription were recorded, most accepted the decision without comment but a few objected strenuously. Several declared that they had lost their previous medications, and one—a patient on welfare—explained that he was going on a long trip.

Another patient, also a welfare beneficiary, told the pharmacist, "I pay taxes too, and I want this medicine."

Discussion

The data obtained in this study have demonstrated that of the 12 agents proposed for particular attention as "dangerous" drugs most likely to be abused, four—hydroxyzine, amobarbital, methylphenidate and mephobarbital—were seldom if ever involved in excessive-quantity single prescriptions.

In striking contract, four other drugs—diazepam, chlordiazepoxide, propoxyphene and phenobarbital—obviously represent a serious problem. These four drugs accounted for 2,989 of the 3,287 single prescriptions calling for excessive quantities.

The addicting properties and the potential for abuse of diazepam, chlordiazepoxide and phenobarbital have long been commonly recognized. Until recently, the potential hazards of propoxyphene have been less widely known, but the problem of propoxyphene toxicity is now a matter of concern.[4,5,6] In the Los Angeles area, and perhaps elsewhere, propoxyphene is now being used by heroin addicts and other drug abusers, who remove the material from the capsules, put it in solution, and inject it intravenously for its psychopharmacological effects.

In the case of multiple prescriptions providing excessive quantities in the possession of a patient, it is clear that the same four drugs—diazepam, chlordiazepoxide, phenobarbital and propoxyphene—figure most prominently, being involved in 272 of the 312 patients concerned in the study.

The ultimate fate of the drugs involved in these excessive-quantity prescriptions is not known. In some cases, the prescribed quantities may actually be ingested by the patients for whom the prescriptions were written. In others, they may be discarded. In some instances, they may be kept in the family bathroom cabinet, providing a lethal invitation to potential suicides and inquisitive children. Some of these excessive quantities may be shared with other members of the family or with neighbors. Some may be sold. Although it cannot be supported by factual evidence, it is commonly believed that not only diazepam, chlordiazepoxide and phenobarbital, but also propoxyphene currently find ready acceptance on the black market.

The fact that only four drugs play such a prominent role in excessive-quantity prescribing, accounting for approximately 90 percent of all excessive-quantity prescriptions unearthed in this study, offers at least a hope that effective control measures can be developed with minimal efforts and with limited interference with normal prescribing patterns. The Medical Center program described here, marked by general cooperation and gratifyingly minor objections from physicians, similarly provides some grounds for optimism. The general acceptance by patients is likewise a hopeful sign. In this respect, it seems important to emphasize that the bulk of the excessive-quantity prescriptions detected at this institution were written by a remarkably small proportion—only about 4 percent—of the staff physicians.

The preliminary control methods described here must obviously undergo many months or years of trial before their value can be fully appreciated. If they are found to be effective, they may well be adapted to use in other hospital settings, with either individual hospital or regional computer facilities employed. It is not clear whether they would be so readily adaptable in the community pharmacy environment.

The cost effectiveness of such control methods is yet to be determined. There is no reason to expect that minimizing the number of excessive-quantity prescriptions by means of a complex computer system can be justified simply on the basis of direct financial savings on the cost of drugs. The major influence of any control method will probably be in the direction of identifying and correcting grossly irrational prescribing, preventing legally prescribed drugs from reaching the black market, and indentifying and eventually treating prescription shoppers and other drug abusers.

Trade and Generic Names of Drugs

Librium®	chlordiazepoxide
Valium®	diazepam
Miltown®	meprobamate
Equanil®	meprobamate
Darvon®	propoxyphene
Seconal®	secobarbital
Mebaral®	mephobarbital

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and legal abortions in San Francisco. Calif Med 117:29-31,
Sep 1972

Obstetricians and Legal Abortions in San Francisco

BARRY BEHRSTOCK, A.B., PAUL MASCOVICH, B.A., DAVID MINOR, A.B.,
AND ARTHUR COLMAN, M.D., *San Francisco*

A STUDY WAS CARRIED OUT to determine the attitudes, the current practices with respect to methods and fees, and the logistics of legal abortion as conducted by obstetricians engaged in private practice in the city of San Francisco.

During 1970 in the city of San Francisco, 7973 abortions were performed, and the ratio of abortions to live births was 532:1000. This contrasts with 4 abortions to 1000 live births reported to the California Bureau of Statistics for San Francisco in 1969.* In 1969, 60 percent of all abortions in California were done in the San Francisco Bay Statistical Area (a nine county area as designated by the California Bureau of Maternal and Child Health) and the ratio of abortions to live births was 115:1000.[1] In 1970, this same area reported only 35 percent of the state's therapeutic abortions yet the ratio increased to 254:1000.[1] Seventeen hospitals in the state recorded more than 1000 therapeutic abortions each in 1970.[1] Four of these hospitals were in the city of San Francisco, contributing significantly to the dramatic 130-fold reported increase in the city's abortions.

Method of Survey

An initial count of all the physicians practicing the speciality of obstetrics and gynecology in the city of San Francisco was obtained through the San Francisco Medical Society directory, the San Francisco telephone directory, and information from private patients and hospitals. The total was 175. Deducted from the list were all specialists who did not consider their practice to be primarily concerned with private patients—33 residents, 25 physicians on the full time teaching and clinical staffs of the University of California and Kaiser Hospitals, nine physicians who had retired and four who had left their San Francisco practices. The remaining 104 obstetricians and gynecologists in private practice were questioned by phone over an eight-week period in the summer of 1971. The questioner (B.B.) identified himself as a medical student studying therapeutic abortion practices in San Francisco. He then asked the physicians if they performed therapeutic abortion as part of their medical practice. Those who said they did were asked the remaining questions. Their responses made up the data of this study. (If, as sometimes happened, they did not have a definite answer to a question, the record in the data was "no opinion" or "no report.")

Of the 104 surveyed, eight were women and 96 were men. Five were Chinese (four of whom were women), six were black and ten had Spanish surnames. The remaining 83 were Caucasian.

From the University of California, San Francisco, School of Medicine.

At the time the article was written the first three authors were second year medical students, Class of 1974. Dr. Colman is Assistant Professor of Psychiatry in Residence.

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Submitted November 22, 1971.

Reprint requests to: Mr. Barry Behrstock, c/o Office of Student Affairs, University of California, San Francisco, School of Medicine, San Francisco, Ca. 94122.

*Due to possible confusion between the Statistics Bureau and city hospitals it is thought that this reported figure is below the actual number performed in 1969.

Results

To the question, "Do you do therapeutic abortions?" 72 or 69.2 percent of the 104 responded "yes," and the responses as related to ethnic background were as follows:

	Yes	No
Black	6	0
Spanish surname	2	8
Chinese	1	4
Caucasian	63	20

The following distribution of responses to nine other questions put to the 72 obstetricians in private practice who stated that they performed legal abortions was recorded:

Question

1. Do you utilize aminocentesis and saline injections?

Yes		No		No opinion	
No.	%	No.	%	No.	%
57	79	15	21	0	

2. Do you believe a psychiatric consultation is necessary for all women?

Yes		No		No opinion	
No.	%	No	%	No.	%
4	5.5	67	93	1	1.5

3. Do you believe in abortion on request?

Yes		No		No opinion	
No.	%	No.	%	No.	%
52	72	18	25	2	3

4. What is the approximate number of therapeutic abortions you perform in an average month?

1-5		6-10		11-19		20		"No idea"	
No.	%	No.	%	No.	%	No.	%	No.	%
37	51	20	28	8	11	4	5.5	3	4.5

5. What do you charge for a therapeutic dilatation and evacuation?

$100-150		$151-200		$201-250		>$250	
No.	%	No.	%	No.	%	No.	%
14	20	32	44	16	22	4	5.5

Varies		No Comment	
No.	%	No.	%
3	4.5	3	4.5

6. Do you perform the procedure on an inpatient or on a "come and go" basis?

>90% in-pt.		>50% to <90% in-pt.	
No.	%	No.	%
23	32	7	10

<50% to >10% in-pt.		<10% in-pt.	
No.	%	No.	%
13	18	29	40

7. What is the approximate percentage of your therapeutic abortion patients sent to you through a referral agency?

25%		26-50%		51-75%		75%		No report	
No.	%	No.	%	No.	%	No.	%	No.	%
25	35	17	23.5	16	22	8	11	6	8.5

8. How long have you been performing therapeutic abortions?

2 years		Since 1967		Before 1967		No report	
No.	%	No.	%	No.	%	No.	%
7	10	27	37.5	34	47	4	5.5

9. What proportion of your therapeutic abortion patients are on Medi-Cal?

25%		26-50%		51-75%		76%		Do not know or no report	
No.	%	No.	%	No.	%	No.	%	No.	%
15	21	24	33	11	15	12	17	10	14

Comments: The legal abortions performed in private practice in San Francisco during 1970-71 were done by 69 percent of the practicing obstetricians in that city. Seventy-nine percent of these physicians will perform amniocentesis and hypertonic saline solution injection for the induction of abortion past the 12th week of gestation. Of the physicians who state that they do not do abortions, 40 percent qualified their answers with statements like, "No, but I refer elsewhere," or "I work through a Catholic hospital and cannot do them," or "I do them only for medical reasons."

Ninety-three percent of the obstetricians performing abortions responded that they do not feel a psychiatric visit is necessary for all women. When asked whether they believe in abortion on request, 72 percent responded yes. Of those responding that they did not, however, 60 percent said that they do approve of abortions if they are agreed upon by both the patient and her physician. Thus, well over 72 percent of the physicians said that they believe therapeutic abortions should be performed when requested by the patient and approved by her physician.

Abortion cases are spread fairly evenly among the obstetricians in private practice, as indicated by the fact that more than 50 percent of the physicians perform five or fewer abortions per month. There are a few physicians performing more than 20 a month. (Of the two general practitioners, not included in this study, who perform abortions in San Francisco, one does more than 150 abortions a month.) The average fee is $185, with 20 percent of physicians charging between $100 and $150. There are currently four physicians charging $100 and four physicians charging $300. Also, none of those charging over $250 will perform abortion by amniocentesis. The trend is toward reducing the charges.

Medical acceptability of abortion as a "come and go" procedure is rapidly increasing in San Francisco with more than 58 percent of the private physicians performing at least half of the procedures on this basis. It was indicated that one common factor preventing this proportion from rising faster is the refusal of most San Francisco private hospitals to permit abortions of that order in their facilities. The general comment from most of the obstetricians contacted was that they would do more "come and go" operations if they were permitted to do so.

There was a disparity between the black obstetricians' willingness to do abortion and that of the Spanish surname and Chinese physicians —all of six Blacks, two of ten with Spanish name, and one of five Chinese. None of the Spanish surname or Chinese obstetricians who would perform therapeutic abortions would do it by amniocentesis.

The abortion-to-delivery ratio in the city of San Francisco (532 to 1000 live births) is more than three times California's average ratio of 172 to 1000.

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Specialty Conference

Catecholamines—A Symposium

Moderator: William D. Odell, m.d., ph.d.

Discussants: George A. Bray, m.d., Vincent DeQuattro, m.d.,
Delbert A. Fisher, m.d., Mark A. Goldberg, ph.d., m.d.,
H. B. McIntyre, m.d., ph.d., William D. Odell, m.d., ph.d.,
Mark A. Sperling, m.d. and Ronald S. Swerdloff, m.d.

This symposium is based on a Teaching Conference held January 25, 1972 at Harbor General Hospital, Torrance

Synthesis, Storage and Secretion of Catecholamines

William D. Odell, m.d., ph.d.*

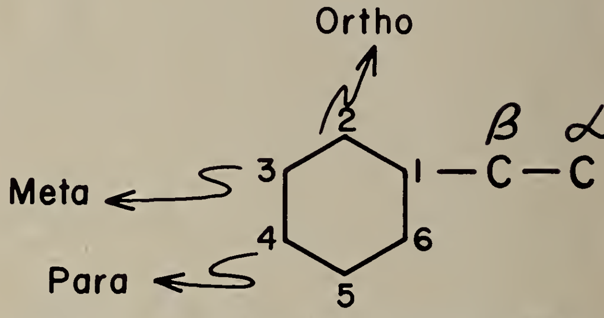

Chart 1.—Chemical coding of phenolic ring and carbon side chain positions in catecholamines. The two side carbons are designated alpha or beta; the phenolic ring position is numbered and also designated "ortho," "meta," or "para." No added designated term is given for positions 5 and 6 since a substitution there would be structurally indistinguishable from one at position 2 and 3; i.e. a meta substitution could be either on 3 or 5 position, and the compounds would be identical.

Catecholamines are dihydroxylated phenolic compounds synthesized in the brain, in sympathetic nerve endings and in cells from the embryonic neural crest (adrenal medulla, organ of Zuckerandl and rests of ectopic neural crest tissue). The physiologically important catecholamines include norepinephrine, epinephrine and dopamine. Chart 1 shows the chemical coding used to designate positions on the skeleton molecule; Chart 2 shows the structures of three catecholamines. A great deal of detailed information is now available concerning catecholamine synthesis; each of the enzymes has been isolated and purified and rate-limiting steps identified.[1] Chart 3 diagramatically depicts the synthetic pathways for norepinephrine (NE) and epinephrine (E). The precursor is 1-tyrosine, which is present in relatively large amounts in blood. Tyrosine is

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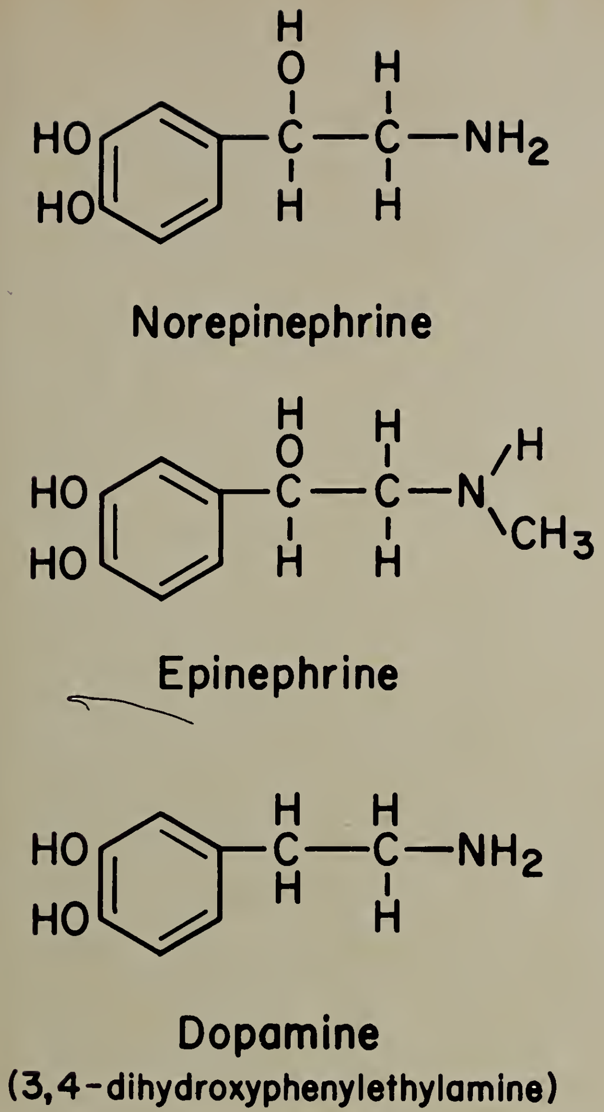

Chart 2.—Formulae of some physiologically important catecholamines synthesized by humans.

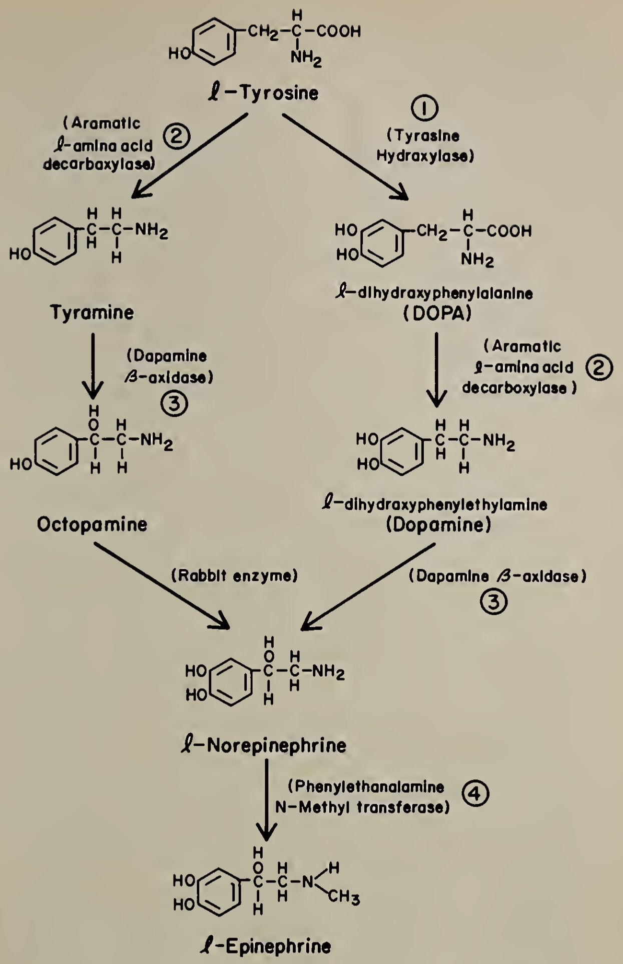
ℓ-Tyrosine
(Aromatic ℓ-amino acid decarboxylase) ②
① (Tyrosine Hydroxylase)
Tyramine
ℓ-dihydroxyphenylalanine (DOPA)
(Dopamine β-oxidase) ③
(Aromatic ℓ-amino acid decarboxylase) ②
Octopamine
ℓ-dihydroxyphenylethylamine (Dopamine)
(Rabbit enzyme)
(Dopamine β-oxidase) ③
ℓ-Norepinephrine
(Phenylethanolamine N-Methyl transferase) ④
ℓ-Epinephrine

Chart 3.—Biosynthesis of catecholamines. The pathway shown on the left has been identified for the rabbit. Based upon present information, the major synthesis in humans probably occurs by the pathway shown on the right. (Drawn from data presented by Melmon, 1968.[1])

obtained from the diet directly or formed in the liver by hydroxylation of phenylalanine. The first step requires transport of tyrosine across the cell and mitochondrial membranes.[2] Within the mitochondria, tyrosine is hydroxylated by the mitochondrial enzyme, tyrosine hydroxylase, to dihydroxyphenylalanine. Tyrosine hydroxylase has considerable substrate specificity but relatively low substrate affinity. This hydroxylation step is rate-limiting, and partial inhibition of the enzyme decreases catecholamine stores.[3] The next step is catalyzed by aromatic 1-amino acid decarboxylase, an enzyme located in large amounts in cytoplasm. This enzyme is present in many tissues and has a high affinity but lower specificity, reacting with several phenolic amino acids.[4] Its normal function is to decarboxylate DOPA to form dihydroxyphenylethylamine (dopamine). Once this compound is formed, it is actively transported to form cytoplasmic particles in sympathetic nerve endings and adrenal medulla. These granules also contain dopamine β-oxidase,[5] a copper-containing enzyme which converts dopamine to norepinephrine. This may also be a rate-limiting step in catecholamine synthesis. In brain, such storage granules are apparently not present. The enzyme dopamine β-oxidase is also found in blood; although its activity in blood has been correlated with disease states, its functional significance is unknown.[6] Some of the storage granules in sympathetic nerve endings and in adrenal medulla contain the enzyme phenylethanolamine-n-methyl transferase which converts norepinephrine to epinephrine.[7] In the newborn infant, this enzyme is usually confined to the organ of Zuckerkandl; after the first year of life it is also found in the adrenal medulla.

The major pathway of catecholamine synthesis thus is believed to be tyrosine⟶DOPA⟶dopamine⟶norepinephrine. Alternative pathways have been described in animals and may also represent significant alternates in man. Note also that synthesis involves considerable intracellular movement of substrates and products—tyrosine across the cell membrane into mitochondria, DOPA back out of mitochondria to cytoplasm, dopamine into storage granules, and eventually release of norepinephrine into the blood stream.

Storage of norepinephrine and epinephrine within granules is believed to be via hydrogen bonding to the phosphorus of adenosinetriphosphate.[8] These represent an important store of potentially active catecholamines, available for release upon demand. Two pools probably exist: one with a relatively long half-life (24 hours), which is not easily available for rapid metabolism, and a second which is readily released from nerve endings by tyramine (discussed later) and which has a half-life of about two hours.[9] Stimulation of sympathetic nerves results in release of catecholamines from both storage sites into the blood. This release is believed to be mediated via acetylcholine and/or the influx of calcium into the granule.

It is possible to inhibit catecholamine synthesis at each of the rate-limiting steps described. From the above discussion, it may be recalled that tyrosine hydroxylase (step 1) catalyzes the major rate-limiting step. This enzyme is inhibited by phenylalanine and also by the drug α-methyltyrosine. These inhibitors decrease norepinephrine synthesis. Alpha-methyldopa inhibits aromatic-1-amino acid decarboxylase (step 2), but since this is not a rate-limiting step, this and similar compounds do not inhibit catecholamine synthesis significantly. This drug is used clinically and is decarboxylated to α-methyldopamine, which is in turn metabolized to α-methylnorepinephrine, a false neurotransmitter. This false neurotransmitter results in norepinephrine depletion, which is responsible for antihypertensive effect; the decarboxylase inhibition is not primarily responsible. Another possible rate-limiting step is that catalyzed by dopamine-β-oxidase (step 3). Disulfiram inhibits this enzyme and also results in hypotension. However, the precise mechanism is uncertain; it is not known that depletion of catecholamine synthesis occurs. Monoamine blocking agents also inhibit this step; tyramine is ordinarily formed and rapidly oxidized as shown in Chart 3. Inhibition of this step 3 results in accumulation of tyramine which is converted to the false transmitter, octopamine. The granules contain both octopamine and norepinephrine which are released by nerve stimulation. Since octopamine is much less potent than norepinephrine, the net effect is a decrease in pressor action.

Agents which inhibit catecholamine effects do so by one or more of four types of actions.[10] Recall that normally epinephrine or norepinephrine or both are synthesized and stored in intracytoplasmic granules. Stimulation results in (a) release from granules, (b) secretion into blood, and (c) subsequent binding to receptor proteins in target tissues. Inhibition of any of these steps may modify norepinephrine or epinephrine action. Thus, if catecholamine storage in granules is prevented or if false neurotransmitters are stored rather than norepinephrine or epinephrine, nerve stimulation fails to release normal amounts of hormone. Prevention of binding to receptor proteins in target tissues also prevents catecholamine action. Table 1 lists the modes of action of such drugs and gives examples of each.

Metabolism and Mechanisms Of Actions of Catecholamines

DELBERT A. FISHER, M.D.* AND
GEORGE A. BRAY, M.D.**

Metabolism:

Small amounts of norepinephrine (NE) probably "leak" into the circulation from sympathetic nerve endings. In addition intermittent

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TABLE 1.—*Mechanisms of Drug Modification of Catecholamine Effects*

Action	*Examples*
I. Inhibition of synthesis	α Methyl-paratyrosine Phenylalanine 3 Disulfiram (antabuse)
II. Inhibition of storage in cytoplasmic granules	Reserpine Guanethidine
III. Synthesis and/or storage of "false neurotransmittors"	α Methyldopa Metahydroxynorephedrine Tyramine* α Methylmetatyrosine
IV. Inhibition of binding to receptor proteins in target tissues	Dibenzyline Phentolamine

*Tyramine is normally synthesized and rapidly degraded. MAO inhibitors block its degradation, and tyramine is metabolized to octopamine and stored.

pulses of NE from nerve endings and epinephrine (E) from the adrenal medulla are released in response to a variety of physiologic stimuli (stress, hypoglycemia, exercise, cooling). Thus the blood levels of catecholamine and the plasma NE:E ratio vary widely throughout the day. Most of our understanding of the metabolism of catecholamines has been derived from the study of exogenously administered tritiated or carbon-labeled compounds. It should be kept in mind that the fate of intravenously administered norepinephrine, as well as some precursors and metabolites, may not accurately represent the fate of endogenously synthesized hormone, since much of the latter is stored or metabolized in and around nerve endings. The metabolism of injected epinephrine probably more closely resembles that of the natural hormone. Tritiated catecholamines disappear rapidly from the circulation; the serum half-life is less than one minute.[9,11] There are three routes for their biologic inactivation: (a) excretion unchanged in urine, (b) uptake by tissues, and (c) enzymatic degradation. Only small amounts of catechols are excreted unchanged in urine. Most of the hormone is rapidly distributed to and taken up by tissues. The proportion of injected catecholamine delivered to a given organ is related to the perfusion of that organ and to the site of injection. The distribution of ^{3}H-norepinephrine in cat tissues two minutes after an intravenous injection is shown in Table 2. At this time heart, spleen, lung and adrenal gland contain the largest amounts of hormone, whereas muscle (diaphragm) and cerebral cortex contain the least. By contrast, when the hormone is injected into the portal vein or given intraperitoneally, most is taken up by the liver, and only a small fraction (15 to 30 percent) reaches the systemic circulation.[12]

TABLE 2.—*Distribution of H^3-Norepinephrine in Cat Tissues 2 Minutes and 2 Hours After Intravenous Administration**

Tissue	*2 minutes*	*2 hours*
Plasma	35	2.7
Heart	156	196
Spleen	229	224
Lung	126	18
Liver	48	23
Kidney	110	27
Diaphragm	10	10
Salivary Gland	46	55
Adrenal Gland	150	176
Pituitary	46	29
Cerebral Cortex	0.6	0.2

*25 μg H^3-norepinephrine/Kg body weight was injected. Results expressed as micrograms hormone/gram tissue. From Axelrod, J Rec Prog Hormone Res 21:597, 1965.

The large amounts of circulating catecholamines taken up by the heart (Table 2) suggest that hormone discharged from the adrenal medulla and adrenergic nerves may serve to replenish or supplement myocardial stores; it is estimated that 20 percent of cardiac catecholamine is derived from the circulation. In contrast, very little of the circulating catecholamine is taken up by brain, presumably due to a blood-brain barrier. The large amounts of catecholamines present in brain appear to be synthesized from

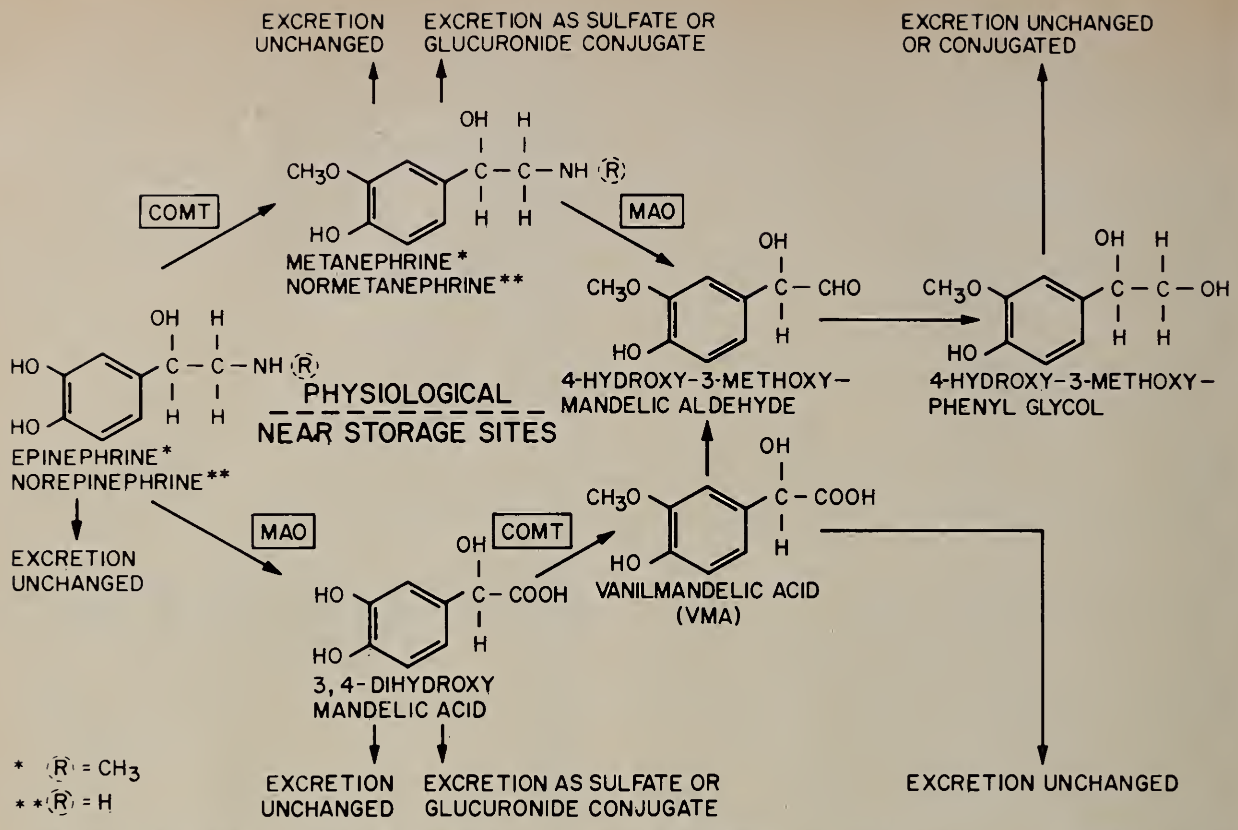

Chart 4.—Pathways for metabolic degradation of catecholamines. The upper portion of the figure shows the major pathway for the metabolism of catecholamines released into the circulation (physiological). The lower half of the figure illustrates the metabolism of catecholamines released intracellularly near storage sites. (Modified from Melmon KL: Catecholamines and the adrenal medulla, *In* Williams RH, Textbook of Endocrinology. Philadelphia, W B Saunders, 1968, page 384)

precursors, such as dihydroxyphenylalanine, which are able to traverse this barrier.

Enzymatic degradation of catecholamines occurs by way of O-methylation and oxidative deamination (Chart 4). O-methylation is catalyzed by the enzyme catechol-O-methyl-transferase (COMT) which stoichiometrically converts epinephrine and norepinephrine to metanephrine or normetanephrine, respectively.[9,11,12] However, the enzyme will catalyze methylation of any catechol, usually in the meta position. COMT is located in the cytosol and is present in most organs including glands, blood vessels, sympathetic and parasympathetic nerves, and brain. Highest concentrations are found in liver and kidney, and most of the catecholamines delivered to these tissues are rapidly transformed to their O-methylated products. Monoamine oxidase (MAO) is the second enzyme system which degrades catecholamines. It is a mitochondrial system which catalyzes the oxidative deamination of monoamines (see Chart 4). MAO is present in most tissues but exists in highest concentrations in and around autonomic nerve endings.

The relative importance of these two degradative pathways has been clarified by use of inhibitors. When COMT is inhibited by pyrogallol, O-methylation is blocked and the effect of administered catecholamines is prolonged; blockade of MAO with iproniazid does not change the effective duration of action of injected catecholamines.[1] Thus, COMT appears to be responsible for the initial enzymatic transformation of circulating catecholamines, whereas MAO plays only a minor role. MAO seems to be responsible for the initial enzymatic degradation of catechols released in and around nerve endings; inhibition of MAO results in an increase in stored catecholamines.[2,12]

The urinary metabolites of ^{3}H-epinephrine appearing over a 54-hour period after intravenous injection of a 1 mg dose of ^{3}H-epinephrine are shown in Table 3. The major metabolites are the O-methylated derivatives and vanillylmandelic acid (VMA). Small amounts of free epinephrine

TABLE 3.—*Metabolism of Epinephrine in Man**

Metabolite	*% Urinary H^3*
Epinephrine	7
Metanephrine	
free	5
conjugated	36
3, 4 dihydroxymandelic acid	
free	0.9
conjugated	0.7
VMA	41
3-methoxy-4-hydroxy-phenylglycol sulfate	7

*H^3 Epinephrine d-bitartrate, 1 mg intravenously over 30 minutes to 12 normal human male subjects. Urine was collected for 54 hours. From Axelrod, J., Rec Prog Hormone Res 21:597, 1965.

TABLE 4.—*Normal Range of Catecholamine and Metabolite Concentrations and Excretion*

Urine:	
Epinephrine – Norepinephrine*	<100 μg/24 hr
Metanephrine – Normetanephrine*	<1 mg/24 hr
Vanillylmandelic Acid (VMA)*	<7 mg/24 hr
3-Methoxy-4-hydroxyphenylglycol	<1.4 mg/24 hr
Blood:	
Epinephrine – Norepinephrine	<1 μg/liter
Adrenal Medulla:	
Epinephrine	0.2 – 0.8 mg/gm
Norepinephrine	0.04 – 0.16 mg/gm

*Normal values from Bio-Science Laboratories. Other values from Melmon, K.L., Textbook of Endocrinology, R.H. Williams (Ed.), W.B. Saunders, 1968, pg. 392.

(7 percent), metanephrine (5 percent), and 3-methoxy-4-hydroxyphenylglycol (7 percent) were excreted; less than 2 percent was oxidatively deaminated to 3, 4-dihydroxymandelic acid. Using a double labeling technique, Kopin[13] simultaneously administered ^3H-epinephrine and ^{14}C-methoxymetanephrine and calculated from the ratios of ^3H:^{14}C and from total radioactivity of each metabolite that 70 percent of circulating epinephrine is O-methylated to metanephrine and only 25 percent is deaminated. Several minor urinary metabolites of catecholamines also have been reported. These include: 3, 4-dihydroxyphenylglycol, N-acetylnormetanephrine, N-methylepinephrine, N-methylmetanephrine, and vanillic acid.[9] The normal range of daily catecholamine and metabolite concentrations and urinary excretion are shown in Table 4.

Tissue catecholamines exist in several forms. Within a few minutes after administration of ^3H catecholamines to rats, large quantities of O-methylated metabolites can be found in tissue.[9,11] Deaminated hormone is present in variable, but small concentrations in and around nerve endings.[9,11,12] Most of the latter hormone is further metabolized to VMA (Table 3). Soon after intraventricular (CNS) administration, several products are formed, including VMA, 3-methoxy-4-hydroxy-phenylglycol, and normetanephrine,[11] indicating that both deamination and O-methylation occur in brain as in other tissues. The catecholamine metabolites diffuse out of tissues into the circulation to appear eventually in urine. Metabolite turnover appears to be rapid from lung, liver and kidney and concentrations are much reduced within two hours after intravenous administration (Table 2). However, concentrations in heart, spleen, salivary gland, and adrenal gland are as high at two hours as at two minutes, suggesting that the amines in these tissues are protected from enzymatic degradation. These tissues, and others with extensive sympathetic innervation, take up circulating catecholamines into the granulated vesicles of sympathetic nerve endings from which the amines are only gradually released and metabolized. Turnover time of most of this hormone, however, is less than 48 hours, since more than 90 percent of an intravenously administered dose of norepinephrine is recovered in the urine within this time.[9] Some tissues, such as brain, may release hormone over a period of many days, but these long half-life pools are small (Table 2).

Many drugs such as cocaine, reserpine, guanethidine, bretylium, imipramine, chlorpromazine, tyramine and amphetamines block the binding of catecholamines to tissues (for example, nerve endings) and thereby increase the sensitivity to catecholamines by increasing their concentration at receptors. These drugs also increase the rate of metabolism of ^3H catecholamines, since the activity of COMT and MAO are not inhibited by these drugs and the unbound hormone is readily accessible for enzymatic degradation.[1]

Alterations in receptor tissues are thought to decrease catecholamine responsiveness in such disorders as metabolic and respiratory acidosis, myxedema, and adrenocortical insufficiency. Cardiovascular sensitivity to catecholamines is

TABLE 5.—*Effects of Adrenergic Stimulation and Administration of Catecholamines*

	Adrenergic Receptor	*Adrenergic Stimulation*	*Epinephrine*	*Norepinephrine*
Cardiac				
Rate	β	↑	↑	↓
Stroke Volume	β	↑	↑	↑
Output	β	↑	↑	↑
Peripheral Circulation				
Arterial Systolic BP	α	↑	↑	↑
Diastolic BP*	α	↑	↑ or ↓	↑
Total Resistance+	α,β	↑ or ↓	↑ or ↓	↑
Cerebral blood flow	α	↓ ±	↑	0 or ↓
Muscle blood flow+	α,β	↑ or ↓	↑	0 or ↓
Splanchnic blood flow+	α,β	↓	↑	0 or ↓
Skin and mucosa blood flow	α	↓	↓	↓
Gut				
Mortility	α,β	↓	↓	↓
Secretion	—	↓	↓	↓
Metabolic Effects				
Oxygen Consumption	β(?)	↑	↑	0 or ↑
Hepatic glycogenolysis	α,β	↑	↑	0 or ↑
Muscle glycogenolysis	β(?)	↑	↑	0 or ↑
Adipose Tissue lipolysis	β	↑	↑	↑

+Over the usual concentration range of circulating epinephrine, the β receptor response (vasodilation) predominates in blood vessels of skeletal muscle and liver and an α receptor response (vasoconstriction) in blood vessels of the abdominal viscera.

* Doses of epinephrine too small to act on α receptors lower blood pressure by β receptor action; larger doses evoke α receptor responses in addition. And the overall effect of full activation of both α and β receptors is an increase in peripheral resistance and consequently a rise in blood pressure. When enough epinephrine has been metabolized to minimize the effect on the less sensitive but more plentiful α receptors, the effect on β receptors persists for a time accounting for the secondary hypotension of the diphasic response.

TABLE 6.—*Classification of Adrenergic Receptors*

	Alpha	*Beta*
Relative Potency of Adrenergic Drugs	E > NE > I	I > E > NE
Examples	Contraction of Arterioles	Chronotropic Inotropic Relaxation of Bronchial Muscles
Blockade	Phentolamine Phenoxybenzamine	Propranolol

greatly augmented in thyrotoxicosis.[1] The mechanism of this latter effect is not clear.[14]

Actions:

The effects of catecholamines are varied and widespread depending upon the site of their release and their local concentrations. In general, stimulation of the post-ganglionic fibers of the adrenergic nervous system produces two types of responses, those which are inhibitory and those which are excitatory. These two kinds of peripheral responses led to an extended search for two hormones which might produce these diverse effects. Such a search, however, was unsuccessful and in 1947 von Euler[15] clearly demonstrated that norepinephrine was the hormone released by stimulation of adrenergic nerves. Epinephrine was the principal hormone of the adrenal medulla, but was not found in nerve endings and was thus not released for local action upon stimulation of adrenergic nerves.

Table 5 summarizes some of the effects which result from stimulation of the adrenergic nervous system and compares them with the response to administration of epinephrine or norepinephrine.[16] The cardiac effects of adrenergic stimulation are mimicked in large measure by epinephrine and in part by norepinephrine. Similarly, the effects on peripheral circulation can be reproduced by epinephrine as well. The metabolic

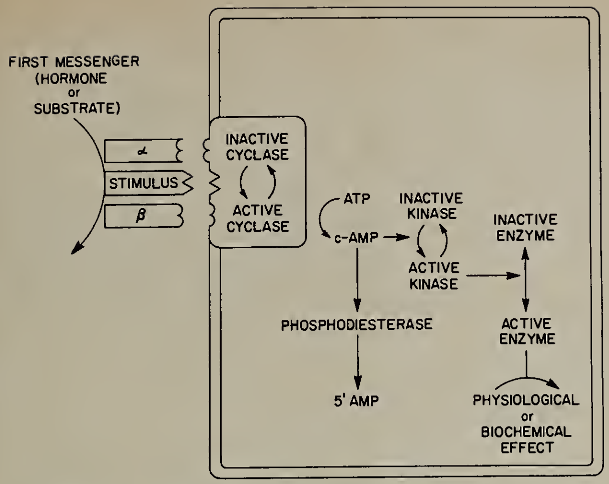

Chart 5.—The second messenger concept. The formation of cyclic-AMP (C-AMP = second messenger) from ATP is increased by interaction of the first messenger with the cell membrane. Adrenergic receptors on the cell surface may modulate the cellular response to the first messenger. Once formed, the cyclic-AMP catalyzes the intracellular events typical of the hormonal response of that cell.

effects on oxygen consumption, glycogenolysis in liver and lipolysis in adipose tissue are primarily produced by epinephrine, with norepinephrine being a weaker drug.

A framework which integrated the excitory and inhibitory responses evoked by stimulating the adrenergic nerves was provided, in 1948, by the experimental work by Ahlquist.[17] This investigator compared the response of a variety of systems both *in vivo* and *in vitro* to six catecholamines. The responses could be divided into two groups depending upon the relative potency of the six catecholamines. For one group, called α-receptor responses (see Table 6), epinephrine was the most potent drug, with norepinephrine somewhat less potent and isoproterenol the least effective. In the second group, called β receptor responses, isoproterenol was the most potent drug, with epinephrine and norepinephrine being weaker agonists. This concept of α and β receptors has been widely extended by the demonstration that drugs can block one or the other of these receptors with a high degree of specificity (Table 6). Phentolamine (Regitine®) and phenoxybenzamine (Dibenzyline®) are potent inhibitors of the α-adrenergic responses while dichloro-isoproterenol was the first of a large series of drugs which blocked the β-adrenergic receptors.

The concept of α and β receptors also has been useful in considering the effects of catecholamines in peripheral tissues. The elegant investigations of Sutherland and his collaborators have suggested a two-messenger hypothesis of hormone action.[18] Circulating hormones or metabolites interact at the cell surface with a specific receptor. In the case of epinephrine or norepinephrine, these receptors are the α and β receptors, but other receptors mediate effects of vasopressin, ACTH, thyrotropin, and gonadotropins (Chart 5). The interaction of the first messenger and the cell wall stimulates an enzyme complex, called adenyl cyclase, to form the intracellular or second messenger, cyclic-AMP (cAMP) from ATP. The primary action of cAMP is to activate protein kinase. In this process, cAMP appears to bind to an inhibitory subunit of protein kinase causing an active, catalytic subunit to dissociate. The active kinase then phosphorylates the inactive form of an enzyme, thereby activating it; alternatively an active form of an enzyme may be phosphorylated and thereby inactivated.[19] For example, in liver the stimulation of cAMP results in protein-kinase mediated activation of phosphorylase and inactivation of glycogen synthetase. In muscle, cAMP (via protein-kinase) also activates phosphorylase and inactivates the active form of glycogen synthetase;[20] whereas in fat tissue, cAMP-activated protein kinase stimulates a triglyceride lipase.[21]

Cyclic-AMP increases in these tissues within seconds to minutes after contact of the first messenger with the target cells. The peak in hepatic cAMP concentration occurs one minute after *in vivo* perfusion with epinephrine, and increased levels of glucose in the perfusate are obvious within 1 to 2 minutes.[19] Cyclic-AMP reaches a peak in fat cells about four minutes after addition of epinephrine to the medium *in vitro,* and glycerol concentrations in the medium begin to increase within 2 minutes.[21]

In many tissues, the adrenergic effects of α and β receptors antagonize one another and modify the effects of other "first messengers." This is clearly illustrated in the case of the pancreas. When epinephrine is infused into normal human subjects (Chart 6), blood glucose rises but there is no increase in serum immunoreactive insulin.[22] When the infusion of epinephrine is terminated, however, serum insulin rises sharply. This inhibitory effect of epinephrine on insulin output during hyperglycemia is mediated through α-adrenergic receptors. This is clearly shown by

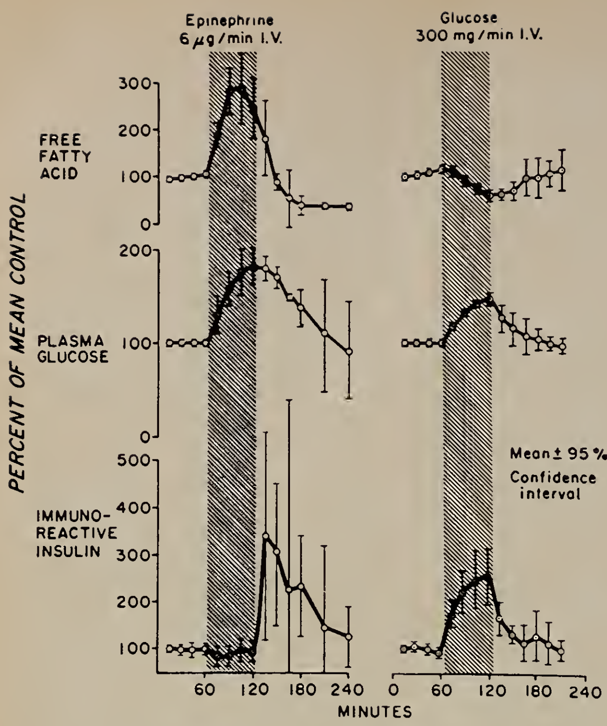

Chart 6.—Effect of epinephrine and glucose on the secretion of insulin. Epinephrine (6 μg/min) increased the concentration of free fatty acids and glucose but insulin concentrations did not rise. An infusion of glucose which produced a lesser increase in blood glucose concentrations produced the expected insulin response. (Reprinted from Porte D, et al: J Clin Invest 45:228, 1966, with permission.[22])

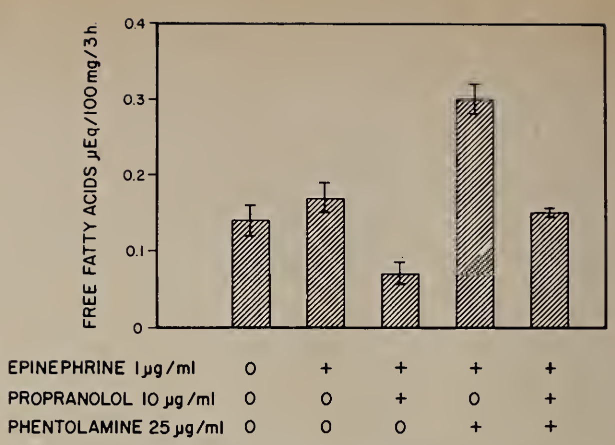

Chart 7.—Effect of adrenergic drugs on lipolysis of human fat. Epinephrine alone had little effect on lipolysis. Propranolol reduced and phentolumine enhanced the lipolytic effects of epinephrine. (Reprinted from Bray GA, Trygstad W: Acta Endocrinologica: In press, with permission.[24])

blocking the α receptors with phenotolamine or phenoxybenzamine. Under these conditions, the infusion of epinephrine is followed by a rise in blood glucose, as well as insulin. These effects also can be shown in studies of isolated rat pancreas.[23] In these experiments, glucose is used as the primary stimulus for the release of insulin; when epinephrine is added to the incubation medium, there is a pronounced inhibition of insulin release. When the α blocker, phentolamine is added, along with epinephrine, the inhibitory effect of epinephrine is abolished. In contrast, isoproterenol had a slight stimulant effect on insulin secretion when incubated with an α blocking drug in addition to glucose. Thus, in the pancreas, glucose mediated insulin release is modulated, both *in vivo* and *in vitro,* by α and β receptor stimulation.

Several other physiological systems show a similar modulation of the action of the first messenger by adrenergic receptors. In human adipose tissue (Chart 7), epinephrine has little or no lipolytic activity by itself even at concentrations far above those present under *in vivo* conditions. However, when an α adrenergic blocking drug such as phentolamine is added, epinephrine stimulates lipolysis; this stimulatory effect of epinephrine can be completely blocked by inhibition of the β receptors. Thus, lipolysis in human adipose tissue is stimulated by activation of the β receptors which increase the intracellular concentration of cAMP[24] and is inhibited by the α adrenergic receptors via mechanisms as yet unclear.

Chart 8 shows the inhibitory effect of norepinephrine on antidiuresis produced by the infusion of vasopressin into water-loaded human subjects.[25] This effect is independent of changes in renal blood flow or glomerular filtration rate[25,26] and can be blocked, in rats or dogs, by phenoxybenzamine, but not propranolol.[26,27] Isoproterenol will produce an antidiuresis similar to that of vasopressin, and this antidiuresis can be blocked with propranolol, whereas the effect of vasopressin cannot.[28] This renal vasopressin (ADH) antidiuresis is mediated by an adenyl-cyclase-plasma membrane receptor. And, as in the pancreas, the effect of the primary messenger, in this case ADH, is modulated by α and β receptors.

Table 7 lists several systems in which antagonism between α and β receptors has been demonstrated.[22-30] In each instance there is a first messenger, such as glucose for the pancreas or vasopressin for the kidney, which is modified by activation of α and β adrenergic receptors. Although the first messenger for the control of food

TABLE 7.—*Modification of Hormone Action by α and β Receptor*

	First Messenger	*Response*	*Modulation of First Messenger by Adrenergic Stimulation*	
			Alpha	*Beta*
Pancreas	Glucose	Insulin Secretion	↓	↑
Kidney	ADH	Water Reabsorption	↓	↑
Ventral Hypothalamus	– – –	Food Intake	↑	↓
Frog Skin	MSH	Darkening	↓	–
Human Fat	– – –	Lipolysis	↓	↑

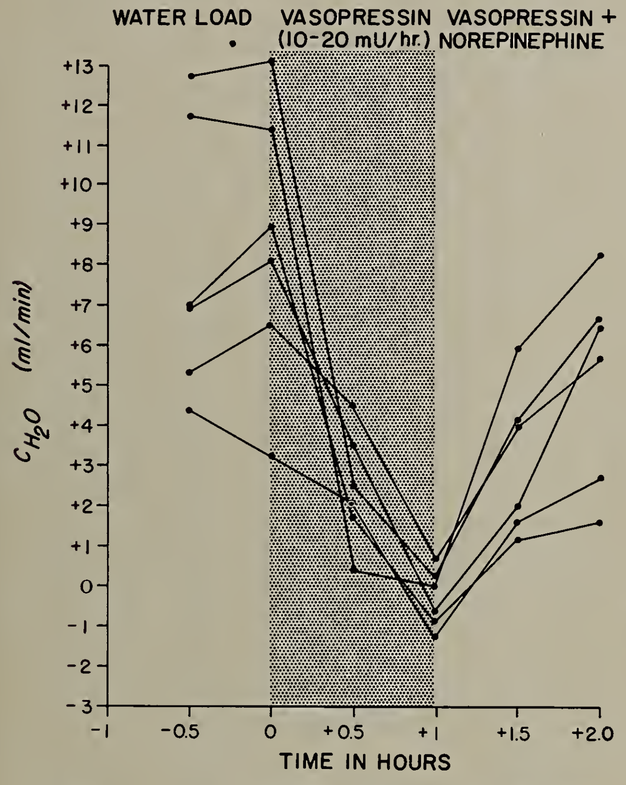

Chart 8.—Norepinephrine inhibition of vasopressin antidiuresis. The effect of norepinephrine on free water clearance during infusion of 10-20 mU vasopressin per hour in water loaded human subjects. After water loading vasopressin was infused for 1 hour and vasopressin plus norepinephrine for an additional hour. (From Fisher DA: J Clin Invest 47:540, 1968, with permission.[25])

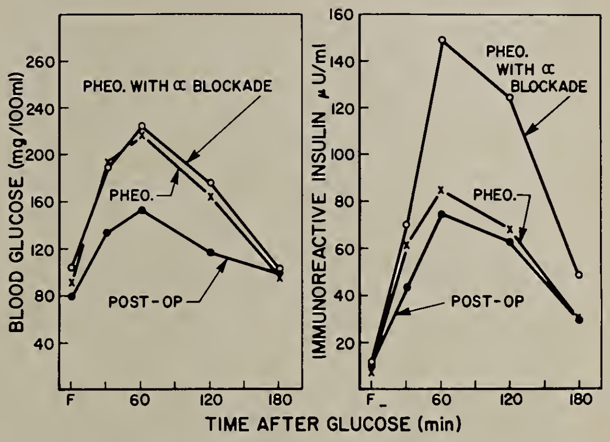

Chart 9.—Mean insulin and glucose levels after an oral glucose load in four patients with pheochromocytoma. Alpha-adrenergic blockade preoperatively did not improve glucose tolerance but the insulin response was significantly augmented. Glucose tolerance post-operatively was markedly improved. (Adapted from Illig R, Ziegler WH: Acta Endocrinologica 66:368, 1971.[31])

intake is unknown, this system is clearly modulated by α and β receptors.[30] Microinjection of norepinephrine into the lateral hypothalamus will stimulate feeding in the rat. Phentolamine (α receptor blockade) will block this effect of norepinephrine but propranolol (β receptor blockade) will not. Conversely, food intake is inhibited by microinjection of isoproteronol into the hypothalamus and this effect is blocked by propranolol. Thus, the hypothalamus has an α receptor mediated system for stimulating food intake (hunger) and a β receptor mediated satiety center.

The role of α and β receptors in human disease is illustrated in patients who have pheochromocytomas. This experiment of nature is similar to the infusion of large amounts of norepinephrine or epinephrine or both. As might be expected from the previous discussion, the changes in blood sugar and insulin will depend upon the level of blood glucose and the relative stimulation or inhibition of α and β receptors. The effect of an oral glucose load on blood sugar and immunoreactive insulin in four patients with pheochromocytoma before and after surgical operation and during pre-operative treatment with phenoxybenzamine is shown in Chart 9. The rise in blood sugar and immunoreactive insulin was significantly higher in the untreated state.[31] Blockade of the α receptors with phenoxybenzamine did not lower the blood sugar before or during the oral glucose tolerance test, but allowed a greater increase in the concentration of insulin. This can easily be understood in terms of the increased stimulation of the α receptors by the high concentrations of circulating catecholamines present in these patients.[32] In the post-operative period when the concentration of circulating catecholamines was reduced, the rises in blood sugar and immunoreactive insulin following administration of glucose orally were significantly reduced.

The polyuria sometimes seen in patients with pheochromocytoma in the absence of glycosuria may be mediated by norepinephrine which inhibits ADH-induced antidiuresis. Thus, an understanding of the interaction of adrenergic receptors and the modulation of physiological systems and hormone actions by these receptors helps explain the varied clinical manifestations often observed in patients with pheochromocytomas.

Role of Catecholamines in Some Aspects of Brain Function

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W. D. Odell, m.d., ph.d.

Parkinson's Disease:

The recognition of dopamine and norepinephrine as transmitter substances at central nervous system synapses has led to a greater understanding of their role in a number of regulatory functions of the brain. This has been most dramatically demonstrated in the case of Parkinson's disease, where rapid translation of basic information into effective therapy has been achieved.

Reserpine, introduced in the early 1950's as a tranquilizer, was found to deplete brain norepinephrine, dopamine and serotonin and to produce an extra-pyramidal disorder similar to Parkinson's disease. Studies of the chemical topography of brain revealed a rather specific distribution of these substances, with highest concentrations in the basal ganglia. The development of fluorescent histochemical techniques by Fuxe et al[33] have led to rather detailed mapping of amine pathways and to the concept of dopaminergic, noradrenergic and serotonergic systems.

Noradrenergic neurons are located in the reticular formation (particularly of the pons and medulla) and in the locus coeruleus. Noradrenergic fibers from the reticular formation pass ventrally through the median forebrain bundle to distribute to the pre-optic area and hypothalamus and ventral stria terminalis and large parts of the limbic system; those fibers originating in the locus coeruleus form a dorsal pathway and distribute to cortical areas. Dopaminergic neurons give rise to a nigro-striatal system and a tubero-infundibular system. In the former, cell bodies located in the substantia nigra send terminals to the caudate and putamen. The tubero-infundibular pathways have their cells of origin in the hypothalamic arcuate nuclei and terminate in the median eminence. In addition, there is some evidence for the presence of a dopaminergic pathway from the ventral portion of the periventricular nuclei to posterior pituitary. The cell bodies of the serotonergic pathways lie in the midline, brainstem raphé nuclei; their projections are to the suprachiasmatic nuclei of the hypothalamus, the limbic system, cerebral cortex, and to the cerebellum. It is also noted there exist descending bulbospinal tracts containing norepinephrine or serotonin.[33,34]

In 1958 Carlson pointed out that the effect of reserpine could be reversed by L-Dopa and suggested that Parkinson's disease was due to a deficiency of dopamine in the basal ganglia. He further speculated that L-Dopa might be useful in the treatment of Parkinson's disease. Hornykiewicz and coworkers had the opportunity to study the brains of patients dying with Parkinson's disease. They found a pronounced depletion of dopamine and its metabolites in the basal ganglia.[35] Subsequently several attempts were made to treat patients with dopamine and dopa and, while transient improvement was recorded, the drug was not thought practical for clinical use. It remained for Cotzias and coworkers to demonstrate that by slowly increasing the dose of L-Dopa to an average of 4 to 6 grams a day a remarkable clinical improvement could be achieved.[36] A complete review of the clinical features of this form of therapy is beyond the scope of this article, but several interesting points should be noted. Excellent reviews of this subject are available.[37,38]

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Dopamine does not cross the blood brain barrier but L-Dopa has rapid access to brain by means of a carrier-mediated transport system similar to that which mediates the penetration of other L-amino amino acids into the central nervous system. After penetration of the blood brain barrier, L-Dopa is converted to dopamine within brain cells. However, it is not known which cells are involved in this uptake. Partially degenerated dopaminergic neurons may be involved or other neurons which normally do not take up dopamine may be altered to function in place of the diseased dopaminergic neurons. Autopsy studies of patients who had received L-Dopa for long periods revealed a mild increase in brain dopamine and pronounced increases in brain homovanillic acid (HVA). Patients receiving L-Dopa have elevated spinal fluid HVA although elevations in dopamine itself in the spinal fluid have not been noted.

Recent studies have focused on the use of dopa decarboxylase inhibitors to reduce the dose and side effects of L-Dopa therapy. This enzyme is ubiquitous in distribution and the orally administered drug is rapidly metabolized to dopamine in peripheral tissue and blood. This excess dopamine is not available to the brain and may be responsible for some of the side effects of therapy. Experimental studies with hydrazine agents which block the peripheral decarboxylase have shown that smaller doses of L-Dopa may be used with some reduction in peripheral side effects.[39]

Involuntary movements which occur in many patients on L-Dopa therapy are frequently the limiting factor in such treatment. Unfortunately these movements are not affected by inhibition of peripheral decarboxylase and remain a major disadvantage to the use of L-Dopa. Amantadine, a drug originally introduced as an antiviral agent, has been found useful in the treatment of Parkinson's disease. It acts to block neuronal uptake of dopamine and therefore makes more of this transmitter substance available for action on receptor sites.

Role in Sleep:

Recent studies on the neurophysiology of sleep have revealed two basic patterns of sleep. Slow waves or non-rapid eye movement sleep is characterized by high voltage slow waves on the electroencephalogram and the usual behavioral correlates which we associate with sleep. Rapid eye movement (REM) sleep, on the other hand, is accompanied by rapid eye movement, loss of muscular tone and superimposed phasic muscular twitches, and an EEG pattern similar to the waking record. These two types occur alternately in cycles of 70-90 minutes. A number of studies have shown similarities in various species which change with brain development.

Early investigators noted that increasing brain amine levels with monoamine oxidase inhibitors lead to an increase in non-REM sleep. In addition inhibition of the synthesis of serotonin by parachlorophenylalanine results in persistent insomnia, which can be reversed by injecting 5-hydroxytryptophan, a serotonin precursor. It will be recalled that serotonergic neurons are localized to some extent in the mid-line raphé neurons and destruction of these neurons causes a reduction in sleep. By contrast, the use of an inhibitor of norepinephrine synthesis, alphamethylparatyrosine, reduces REM sleep without effect on non-REM sleep. Destruction of the lateral noradrenergic neuron will also reduce REM sleep. We are only beginning to understand the clinical implications of these findings. For example, some patients with narcolepsy have been found to enter REM sleep very rapidly and the hypnogogic phenomena associated with this syndrome are similar to the tonic phases of REM sleep. Amphetamines, the usual treatment for narcolepsy, are noradrenergic stimulants.[40]

The Role in the Control of Gonadotropin Secretion:

The control systems governing reproductive functions are extremely complex. Chart 10 depicts schematically the female reproductive system. Gonadal steroids (both estrogen and progestin) exert both positive and negative (stimulatory and inhibitory) effects on LH and FSH secretion, and a reproductive cycle (in humans, the men-

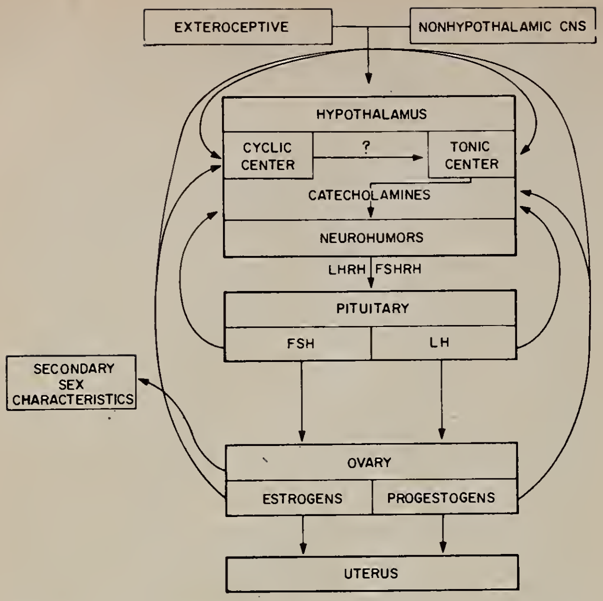

Chart 10.—Schematic presentation of the Hypothalamic-Pituitary-Ovarian System in women. Modified from Odell and Moyer, 1971. (Reference: Odell WD, Moyer DL: Physiology of Reproduction. St. Louis, The C. V. Mosby Company, 1971)

strual cycle) involves a complex interplay of rising and falling specific gonadal steroids, fluctuating CNS neuronal or neuro-humoral mediators, hypothalamic releasing factors and pituitary LH and FSH. It is beyond the confines of this review to discuss reproductive physiology. Suffice it to say that considerable evidence now indicates that catecholamines act as messengers in this system.[41] Catecholamines are unevenly distributed in the brain, and appear to be concentrated within certain regions probably related to endocrine function.[42] Klaiber et al[43] reported that monoamine oxidase activity varied in peripheral blood during the menstrual cycle in women. Activity was low just preceding ovulation when estradiol concentrations were highest and progesterone concentrations were low; and highest post ovulation when progesterone concentrations were high. Reserpine, which depletes catecholamine stores, causes amenorrhea in women and also prevents ovulation in rats. In rats in 1966 Kobayashi et al[44] showed that hypothalamic MAO activity varied during the estrus cycle: Activity was increased in proestrus and in response to castration. Estrogen treatment of castrated rats suppressed LH and FSH and also prevented the rise in MAO activity in hypothalamus. MAO activity in the cerebral cortex did not change during these manipulations. Donoso et al[45] showed the norepinephrine content of the hypothalamus also varied during the estrus cycle paralleling MAO activity. Estrogen treatment also returned hypothalamic norepinephrine to normal in castrate rats. Kamberi et al[46] infused dopamine, epinephrine, or norepinephrine into the third ventricle, pituitary stalk or anterior pituitary: 1.25 μg of dopamine increased serum LH 400 percent in 10 minutes, 900 percent in 20 minutes, and 2000 percent by 120 minutes. Infusion of epinephrine or norepinephrine did not affect serum LH; infusion of dopamine directly into the pituitary also had no effect on serum LH. Kamberi et al[47,48] subsequently showed dopamine also caused increased follicle stimulating hormone and luteinizing hormone releasing hormones (LHRH) in portal vessels of the pituitary. Recent evidence indicates that there is one releasing hormone which affects pituitary secretion of both LH and FSH.[49] Thus, these two studies are internally consistent. Measurement of the LH releasing factor directly has apparently not been performed.

Pheochromocytomas

RONALD S. SWERDLOFF, M.D.*

Pheochromocytomas are catecholamine-producing tumors derived from chromaffin cells. A very large majority of these tumors are found in or adjacent to the adrenal glands,[50-52] and the remainder are located at any site where chromaffin tissue is found. (Figure 1 illustrates the varied locations.) For unknown reasons, non-familial pheochromocytomas arise in the right adrenal gland twice as frequently as in the left.[51,53] The most common extra adrenal location is the organ of Zuckerkandl (the sympathetic plexus adjacent to the origin of the inferior mesenteric artery). Other locations include the remaining abdominal preaortic regions, urinary bladder,[54] thorax,[55] cervical region,[56] brain,[56,57] kidney,[58] hilum of the liver[59] and ovary.[60] Unusual locations include the glomic tissue present

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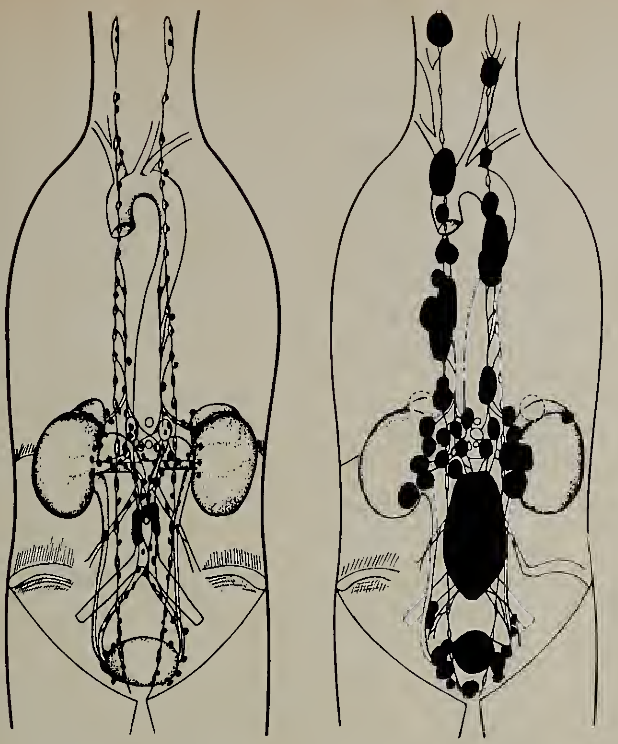

Figure 1.—Left, anatomic distribution of chromaffin tissues in the newborn. Right, the location of extra-adrenal pheochromocytoma reported in the literature. (Published with permission from Page LB, Copeland, RB, 1968.[71])

at the carotid bifurcation, along the arch of the aorta, in the areas of the vagus nerve, at the bulb of the jugular vein and along the femoral vessels.[61]

The tumors vary in size from a few grams to several kilograms;[62] in some series up to 15 percent are palpable.[50] Multiple tumors occur not infrequently,[51] with the highest incidence in children[62] and those with familial predilection for the disease.[62,63] Most pheochromocytomas appear benign histologically; however, between 2.5 and 15 percent (in different series) of reported cases ultimately metastasize to distant sites.[50,64-66] Since benign tumors are often not reported, an incidence of about 1 percent may be more accurate.[62]

Pheochromocytomas occur in approximately equal frequency in both sexes and are found over a wide age range, with the highest incidence occurring in the 30 to 50 age group. The occurrence of these tumors in the general population is quite low and the published incidence amongst hypertensive patients varies from 5 percent to a small fraction of 1 percent.[53,67] The latter estimate is undoubtedly closer to reality.

Since the successful surgical removal of a pheochromocytoma by Mayo in 1927,[68] these fascinating tumors have engendered an especially great interest amongst physicians and surgeons. Despite this interest, the reasons for difficulty in diagnosis include: (a) their relative rarity in an otherwise overwhelmingly large hypertensive population, and (b) the varied presentations, which often suggest other disorders such as hyperthyroidism, diabetes mellitus, essential hypertension, psychoneurosis, primary cardiac disease and even carcinoid syndrome. The importance of the diagnosis, however, is apparent when one considers the high mortality in untreated cases, the potentially curable nature of the disease[20] and the necessity for detection if associated familial disorders, including patients with medullary carcinoma of the thyroid (see below), are to be recognized and treated appropriately.

Clinical Manifestations of Pheochromocytomas:

The clinical manifestations of this disease are almost invariably related to the effect of increased catecholamines. The effects may be α adrenergic, β adrenergic or the combined effect of both, and may involve the autonomic nervous system as well as the central nervous system.

Tables 4, 5 and 6 describe some of the α and β adrenergic effects of catecholamines and emphasize the frequently antagonistic nature of the two types of receptors. Epinephrine and norepinephrine stimulate both α and β receptor activities, but in the case of epinephrine, β stimulation predominates; while with norepinephrine there is greater α receptor activity.

In pheochromocytomas, the biosynthesis of the catecholamines proceeds along the same pathway as normal catechol secreting tissue (Chart 3). These tumors may secrete norepinephrine, epinephrine or, more commonly, both. Those tumors which produce predominately epinephrine usually arise within the adrenal gland; tumors producing exclusively epinephrine are rare. The symptoms produced are to a large extent the result of the amount and proportion of norepinephrine and epinephrine secreted by each tumor although individual variation in responsiveness must also exist. Since so many bodily functions are under the influence of the catecholamines, the great variety of clinical manifestations with

TABLE 8.—*Symptoms in 100 Patients with Pheochromocytomas*

Symptoms	*(%)*	*Symptoms*	*(%)*
Headache	80	Numbness or Paresthesia	11
Perspiration	71	Blurring of Vision	11
Palpitation (with or without tachycardia)	64	Tightness in Throat	8
Pallor	42	Dizziness or Faintness	8
Nausea (with or without vomiting)	42	Convulsions	5
Tremor or Trembling	31	Neck-Shoulder Pain	5
Weakness or Exhaustion	28	Extremity Pain	4
Nervousness or Anxiety	22	Flank Pain	4
Epigastric Pain	22	Tinnitus	3
Chest Pain	19	Dysarthria	3
Dyspnea	19	Gagging	3
Flushing or Warmth	18	Bradycardia	3
		Back Pain	3

From Thomas JE, Rooke ED and Kvale WF: The neurologist's experience with pheochromocytoma, J.A.M.A. 197:754, 1966.

TABLE 9.—*Clinical Aspects of Pheochromocytoma*

Paroxysmal Hypertension	26.4%	134		
Permanent Hypertension	60.5%	307	With Crises	137
			Without Crises	170
Hypertension of Pregnancy	3.5%	18		
Atypical Semeiology	3.9%	20	Paroxysmal Signs	14
			Permanent Signs	4
			Endocrine Signs only	2
No Clinical Signs (total number of cases without hypertension 48 or 4.9%)	5.5%	28	Discovered by chance	13
			Medicolegal form	9
			Local Signs (benign or malignant)	6

Herman & Mornex, Human Tumors Secreting Catecholamines, 1964.[70]

which pheochromocytomas present is not surprising.

Table 8 describes the individual symptoms found in 100 patients[52] with this disorder, but fails to describe the wide variability in combinations of these symptoms seen in any given patient. The classic description of pheochromocytomas is that of a paroxysmal disorder due to intermittent secretion of catecholamines, yet half or more of all patients[67] have sustained hypertension and up to 40 percent have no evidence of episodic symptoms[70] (Table 9).

Paroxysmal Hypertension. The hypertensive episodes are often severe, the diastolic blood pressure may suddenly reach 180 mm of mercury. These attacks are frequently associated with intermittent headache, palpitations with or without tachycardia, excessive perspiration, nausea and pallor. Vague emotional abnormalities, anxiety, tremor, chest and abdominal pain, flushing, visual blurring and paresthesias are not uncommon. Episodic symptoms may be dissimilar in different subjects but tend to be uniform in character in a given patient. Typically their onset is abrupt and sometimes explosive. The duration of individual attacks is from seconds to days. Fifty percent last less than 15 minutes.[71] The frequency of attacks may vary from less than one per year to many per day. The appearance of attacks after periods of rest or sleep is frequently noted and specific activities may precipitate them[72] (Table 10). The attacks may terminate suddenly with a flush replacing the earlier pallor, followed by a feeling of well-being. More commonly the crisis is followed by extreme asthenia, which persists until the next paroxysm or disappears slowly over a period of several hours.[70]

Sustained Hypertension. Patients with sustained hypersecretion of catecholamine usually present with persistent hypertension and hypermetabolism characterized by tremulousness, fe-

TABLE 10.—*Factors that Precipitate Paroxysms in Patients with Pheochromocytomas*

Change of posture (bending, stooping, lateral flexion)
Exertion
Trauma to side or abdomen (including massage)
Local heat
Perirenal air insufflation
General Anesthesia
Parturition
Meals
Alcohol
Histamine (as in gastric analysis)
Amobarbital sodium sedation
Tetraethylammonium
Pain
Hyperventilation
Emotional stress
Carotid sinus pressure
Change of temperature
Sleep
Laughing
Sexual intercourse
Shaving
Gargling
Straining at stool
Sneezing
Having blood pressure taken
Urination (pheochromocytoma of the bladder)
Prophylthiouracil
Corticotropin
Smoking
Glucagon

From Moorhead, E.L. et al., JAMA 196:1107, 1966[72]

ver, excessive perspiration and weight loss or inability to gain weight.[71] Orthostatic hypotension is commonly found in patients with sustained hypertension. These patients may have intermittent further increases in their catechol secretion and may have superimposed paroxysmal symptoms similar to those with only intermittent catechol hypersecretion.

Hypotension. While hypertension either sustained or paroxysmal is found in 90 percent of patients,[70] a few patients may present with severe paroxysmal hypotension[73] and shock. These patients have been demonstrated to secrete a high epinephrine to norepinephrine ratio with the β adrenergic effect of peripheral vasodilation predominating. As would be expected, other epinephrine induced symptoms may be found in association with the grave appearance of shock of these patients.

Sweating. Perfuse perspiration is an extremely common manifestation of pheochromocytomas; it has been reported in from 60 to 100 percent of cases.[74] It has been suggested that there often is a peculiar head, neck and upper thorax distribution of the perspiration.[71]

Headaches. Headaches are probably the most common symptom of this disease. They are often abrupt in onset, severe and throbbing in nature, bilateral in location and of relatively short duration. In some patients, however, they may be indistinguishable from ordinary hypertensive headaches. In at least one series, headache was the sole symptom in 10 of 100 patients.[52]

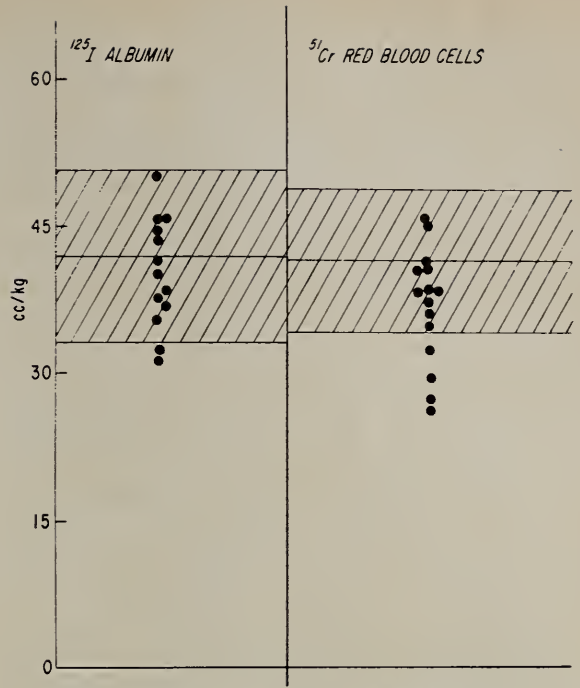

Chart 11.—Plasma volumes of patients with pheochromocytoma before therapy as estimated with ^{125}I-albumin or ^{51}Cr red blood cells or both. Twenty-eight studies were performed in 18 patients. (From Sjoerdsma A, Engelman K, Waldmann J, et al[66])

Orthostatic Hypotension. This is a predominant finding in many patients with pheochromocytoma. Early literature suggested that this might be due to relative refractoriness of postural reflexes owing to constant exposure to high circulatory levels of norepinephrine. This theory was displaced by the suggestion that patients with pheochromocytomas frequently have a reduced plasma volume as well as a significantly reduced total blood volume and that hypovolemia was a major factor in the production of orthostatic hypotension. However, studies by Waldman[66] demonstrated that plasma volume was reduced in only four of 18 patients with untreated pheochromocytomas (Chart 11). Three of these four patients had metastatic disease. Based on this data, it appears that while reduced blood volume may occur in pheochromocytomas, especially in patients with malignant disease, the majority of the patients have normal blood and plasma volume values. The pathophysiologic mechanisms involved in orthostatic hypotension remain unclear.

Myocarditis. It is now recognized that in addition to the hypertensive heart disease seen in the patients with long-standing profound hypertension, a distinctive histologic type of myocarditis may be seen in patients with pheochromocytomas. In one study, Von Vliet and associates[75] reported that over half of 26 patients with pheochromocytoma examined post-mortem had evidence of myocarditis; and a majority of those in whom that evidence was present also had evidence of left ventricular failure and pulmonary edema. The same authors demonstrated that administration of norepinephrine in large doses to experimental animals could produce a similar histological picture. It must be recognized, however, that patients with pheochromocytomas may develop cardiac arrhythmias on the basis of the pharmacological effect of catechol hypersecretion independent of evidence of myocarditis.

Abnormal Carbohydrate Metabolism. Impaired carbohydrate metabolism is common in patients with pheochromocytomas.[71,76,77] The degree of impairment may be great enough to produce fasting hyperglycemia and glycosuria which is reversible after surgical removal of the tumor. These abnormalities (see discussion under catecholamine action) have been ascribed to α adrenergic impairment of insulin release,[76,77] increased resistance to insulin action[76] and increased glycogenolysis.[78] In patients with preexisting mild diabetes, the presence of pheochromocytoma may cause severe exacerbations with ketoacidosis and other diabetic complications.

Weight Loss. The lean body habitus of patients with pheochromocytomas has been emphasized by many authors.[53,64,79] This tendency to be underweight is related to the hypermetabolic effects of catecholamines and specifically to increased lipolytic activity.[80,81] The clinical axiom that patients with pheochromocytomas are never obese, however, was dispelled by Lee and Rousseau[81] in 1966 when they reported eight of 22 patients with pheochromocytomas were overweight by 10 percent or more. It is of interest that those who were lean had sustained hypertension, while those with obesity had paroxysmal symptoms.

Vasomotor Phenomenon. Pallor of the face or hands is a common symptom[52,74] due to the vasoconstrictive action of catechols on superficial vessels. This may be followed in some patients by flushing and a feeling of warmth in the face.[52,72,74] Ischemia of the toes,[72] intermittent claudication[82] and Raynaud's phenomenon[72] may also be seen in some patients.

Gastrointestinal Symptoms. The gastrointestinal manifestations of pheochromocytomas are diverse. Nausea, vomiting and abdominal pain are well recognized manifestations of the disease,[52,72] others such as obstipation,[64,83] megacolon,[83] ischemic enterocolitis[83] and perforation[84] are much less common. The catecholamines affect gastrointestinal physiology through relaxation of intestinal smooth muscle, decrease in frequency and intensity of peristalsis and vasoconstriction of splanchnic anterioles.[85]

Familial Pheochromocytomas:

In some families there appears to be a genetically determined tendency to develop pheochromocytomas which is inherited as an autosomal dominant in character. These patients differ from those with sporadic disease in that they have a much higher incidence of multiple tumors.[51] Those with a solitary tumor do not have the right-sided predominance of adrenal involvement. The diagnosis tends to be made earlier and may be associated with the neurocutaneous syndromes or with multiple endocrine abnormalities including medullary carcinoma of the thyroid.

Pheochromocytoma Associated With Pregnancy:

Pheochromocytomas often represent an extremely dangerous complication of pregnancy.[71] Mortality figures for both fetus and mother approximate 50 percent. The manifestations of pheochromocytoma in pregnancy may be confused with toxemia and in the postpartum period with uterine rupture. Because of the grave effects of delivery in these patients, diagnosis and operative treatment should be carried out as soon as possible. If the patient is near term, removal of the tumor and cesarian section should be done at the same time.

Neurocutaneous Syndromes:

The neurocutaneous syndromes include neurofibromatous, von Hippel-Lindau disease, Sturge-Weber syndrome and tuberous sclerosis. These are thought to be disorders in embryologic development of the primitive neuroectoderm which also gives rise to the chromaffin tissue.

Neurofibromatosis is a disorder which may include the following manifestations: neurofibromata, *café au lait* spots, axillary freckling, generalized hyperpigmentation, mental retardation, meningiomas, gliomas and congenital vertebral abnormalities. The incidence of pheochromocytomas in these patients has been reported to be between 4 and 25 percent.[53,86-89] This disease complex may occur with only minimal physical findings such as several *café au lait* spots and hypertension.

Von Hippel-Lindau disease consists of angiomatosis retinae and hemangioblastomas of the cerebellum. The incidence of associated pheochromocytomas is not known, but a number of cases have been reported.[90,91]

Medullary Carcinoma of the Thyroid and Pheochromocytomas:

The association of these two tumors has received considerable attention in the last few years.[92-95] They may present with associated mucocutaneous abnormalities including those described above, hypocalcemia, parathyroid adenomas or hyperplasia, Cushing's syndrome or a carcinoid-like syndrome.

The thyroid tumors are derived from the perifollicular or calcitonin secretory cells of the thyroid,[63,96-98] and would therefore appear to be embryologically derived from the ultimobranchial body which is endodermal in origin. However, these tumors stain positively with chromaffin salts[99] and recent evidence indicates that the C-cells are in fact derived from migratory neuroblastic elements or neural crest tissue,[100,101] thus confirming medullary carcinoma as a disorder of neuroectodermal cells.

Medullary carcinomas of the thyroid are usually multicentric in origin and may metastasize widely to other organs.[95] They have been demonstrated to contain calcitonin in high concentrations in the tumors as well as in peripheral serum.[95,102-105] Hypocalcemia has been reported[95,103,106,107] and it has been suggested that the associated parathyroid hyperplasia and adenomas,[95,106,108] may be the result of prolonged stimulation due to the calcitonin-induced decrease in serum calcium.[106] Cushing's syndrome has been described. These findings have been attributed to ectopic ACTH production from either the thyroid or adrenal neoplasm.[95,109,110] A diarrheal syndrome[95,104] sometimes associated with flushing[111] has been reported which may be due to prostaglandin secretion from the thyroid tumor.[112] A separate syndrome consisting of multiple mucosal neuromas and peculiar physiognomy in addition to medullary carcinoma and pheochromocytomas has also been described.[100]

Disorders of Catecholamines in Childhood

Mark A. Sperling, m.d.*

Disorders of catecholamine metabolism in childhood comprise a spectrum of diseases exemplifying excessive, disordered and inadequate production of the sympathomimetic amines.

Overproduction:

These disorders include pheochromocytoma, neuroblastoma, and ganglioneuroma. Pheochromocytoma has already been discussed. In general the features described for adults apply equally well to children. Significant differences include multiplicity of tumors in 25 percent of cases, compared with only 4 percent in adults,[113] the presence of sustained rather than paroxysmal hypertension, and weight loss as a major symptom.

Neuroblastoma and ganglioneuroma are both functioning endocrine tumors producing catecholamines. Consideration of their embryonic origin from neural crest ectoderm permits understanding of their distribution, function and symptoms. Thus, (a) they will be found throughout the body wherever sympathetic neural cells migrate (Figure 1), (b) they will not be able to proceed beyond norepinephrine synthesis, because they lack the enzyme phenylethanolamine-N-methyl transferase, which is present in the adrenal medulla and which controls conversion of norepinephrine to epinephrine (Chart 3) and (c) some of the symptoms produced will be directly related to the secretion of excessive quantities of catecholamines. Moreover, assessment of cate-

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cholamine metabolism can be utilized for diagnostic, therapeutic and prognostic purposes.

Neuroblastoma is one of the most common soft tissue malignant neoplasms of infancy and childhood. It accounts for 8 percent of deaths from cancer in children. Estimates of its incidence suggest 5 to 10 new cases per million children under the age of 15 years. One-third are diagnosed in the first year of life. This neoplasm spreads by invasion of local tissues and by hematogenous and lymphatic dissemination. The latter results in widespread secondary tumor in regional lymph nodes, skeleton, bone marrow and liver, often before the primary lesion is evident. In one large series of 217 cases, 70 percent of children had metastasis at the time of initial diagnosis.[114] Most commonly the primary site is the adrenal medulla or the sympathetic chain in the chest or abdomen. Multiple primary sites in the same person and an association with neurofibromatosis have been described.

Pathology. Microscopically, the tumor is composed of immature neuroblasts and nerve fibrils arranged in sheets or rosettes. If, in addition, the tumor contains ganglion cells, it is called a ganglioneuroblastoma and carries a better prognosis. However, the best prognosis exists for tumors containing only mature ganglion cells, a ganglioneuroma. Neuroblastoma is a tumor restricted almost entirely to the first decade of life with a peak incidence at three years.

Clinical Features. These may be widely varied. A most common presenting complaint is an abdominal mass, often discovered on routine examination. Enlarged lymph nodes, hepatomegaly, skull masses, or unilateral proptosis with ecchymosis and periorbital swelling are other common presentations. Symptoms are unusual in the early course of the disease. Later there may be bone pain, painful joints, pyrexia of unknown origin, irritability, weight loss, and anemia. Differentiation from leukemia, Wilm's tumor or arthritis may be necessary. Affected children excrete increased amounts of catecholamines in their urine, but symptoms related to increased sympathetic activity are unusual. Occasionally, however, a child manifests paroxysmal hypertension, flushing, tachycardia, sweating and irritability, identical to the symptom complex produced by pheochromocytoma in adults or children. An interesting association is that of chronic diarrhea with ganglioneuroma. VMA excretion in the urine is decidedly increased preoperatively. Dramatic disappearance of symptoms and return of catechol excretion to normal follows successful removal of the tumor. Clinically, the diarrhea simulates that of malabsorption, although it tends to be more watery and results in greater fluid and electrolyte losses. Symptoms of catecholamine oversecretion can occur but are infrequent and a major diagnostic clue is resistance to the usual medical measures. There is no direct correlation of the symptoms with the magnitude of urinary catecholamine excretion.

Diagnosis. Diagnosis may be made from histological examination of biopsy material or by radiological techniques which may reveal calcified areas in the abdomen, displacement of kidneys on intravenous pyelogram or a moth-eaten appearance and periosteal reaction of metastatic lesions to bone. The most useful and definitive aid to diagnosis is the measurement of urinary catecholamines, which are almost always increased in affected children. However, the patterns of urinary metabolites vary.

Twenty percent of patients have increased HVA and dopamine excretion but normal VMA and normetanephrine (see later sections of this symposium). Others have elevated VMA with no other catecholamine abnormality. Thus, a single determination of VMA or HVA may be normal and therefore misleading. On the other hand, the presence or reappearance of elevated urinary catecholamine secretion signifies the presence or recurrence of the disease, even when all other diagnostic tests are normal. The precautions for false positive and false negative tests are discussed in the following section. Two recent papers extensively review the literature on neuroblastomas[115] and on catecholamine excretion in this condition.[116]

Disordered Metabolism—Familial Dysautonomia:

Disordered catecholamine metabolism is exemplified by familial dysautonomia. This condition was first described by Riley, Day, Greely and Langford in 1949[117] and bears the eponym Riley-Day syndrome. Over 200 patients from 164 sibships have subsequently been described from North America alone.[118] The typical history includes the following: Beginning in early infancy the affected child has difficulty in feeding and swallowing, with frequent regurgitation and aspiration. Within the first two to three years,

TABLE 11.—*Clinical Features of 23 Cases of Familial Dysautonomia*

Feature	*Number Affected*	*Feature*	*Number Affected*
Sex distribution—males females	12 11	Erratic temperature control	18/22
Absent or reduced fungiform papillae	23	Excessive salivation	18
Excessive perspiration	23	Excessive vomiting	17
Vasomotor instability	23	Scoliosis	16
Pathological histamine response	20	Pulmonary infection	15/22
Psychomotor retardation	19	Swallowing disturbances	13/17
Dysautonomic facies	20	Corneal ulcers	12
Hypoesthesia	18/21	Ataxia	11/15
		Dysarthria	11/14

From Moses et al., Israel J Med Sci 3:358, 1967[119]

the lack of tearing, relative insensitivity to pain, emotional liability, breathholding attacks, episodic vomiting, unexplained high fever, skin blotching, excessive sweating, and motor incoordination become manifest. Later, postural hypotension and paroxysmal hypertension may appear. By age ten, many show kyphoscoliosis and growth is poor. Fungiform papillae on the tongue are absent (or greatly reduced) and patients assume a typical facial appearance, with a transverse mouth, a tendency to facial drooping, hypertelorism, external strabismus, and a frozen appearance with an empty look. Sexual development is normal and there appears to be no endocrine dysfunction. Neurologically, there is reduced sensitivity to pain, absence of gag reflex and of deep tendon reflexes in some and a positive Romberg sign and ataxia of cerebellar origin. The voice has a nasal quality and older patients have Charcot neuropathic joints. A classic sign is the absence of the triple response to scratching—a thin red line only, but no flare. Similarly, the flare is absent following injection 0.1 ml of 1:1000 histamine hydrochloride intradermally. By contrast, the response to mecholyl or norepinephrine is greatly exaggerated, and restoration of taste or reflexes has been observed following mecholyl injection. The major clinical features are summarized in Table 11.

Twenty-five percent of affected patients die before age ten, and 50 percent are dead before age 22. As is evident from the wide array of symptoms and signs, there are abnormalities of the autonomic, sensory, and central nervous system, and cytologic changes of swelling and degeneration have been observed in the hypothalamus, brain stem and autonomic ganglia.

The disease is confined almost exclusively to one ethnic group, Ashkenazi Jews, and all genetic data is compatible with an autosomal recessive mode of inheritance. In the group at risk, the gene frequency has been estimated to be 0.01 by two different investigators[118,119] and the incidence to be 1:10,000-20,000 births. This type of inheritance is, of course, very suggestive of an enzyme deficiency. In addition, the alterations in urinary excretion of norepinephrine and its metabolites[120] also support or imply a disorder of the sympathetic system. Table 12 summarizes several of these studies. As can be seen, urinary excretion of VMA, the major metabolite of norepinephrine is decreased, while urinary HVA, the major metabolite of dopamine, is increased. The most recent of these studies[122] investigated noradrenalin synthesis and dopamine metabolism following injection of labeled dopamine in three patients with familial dysautonomia and six normal controls. They again confirmed a significant reduction of norepinephrine synthesis from its precursor dopamine, as reflected in urinary metabolites, and in the incorporation of labeled dopamine to labeled norepinephrine as follows:

	Percent infused dopamine in norepinephrine & metabolites	*Percent infused dopamine in dopamine and its metabolites*
Normal	25	75
Familial Dysautonomia	15 to 20 Turnover normal	80 to 85

These studies would suggest a block in the conversion of dopamine to norepinephrine, a step

TABLE 12.—*Catecholamine Metabolism in Familial Dysautonomia*

Reference	*Urinary VMA (Norepinephrine)*	*Urinary HVA (Dopamine)*	*Dopamine β Hydroxylase*
Smith et al. New Engl J of Med 268: 705, 1963	decreased	increased	presumed decreased
Moses et al. Israel J Med Sci 3: 358, 1967	decreased	normal	possibly decreased
Gitlow et al. Pediatrics 46: 513, 1970	decreased	increased	presumed decreased
Goodal et al. J Clin Invest 50: 2734, 1971	decreased	increased	presumed decreased
Weinshilboum et al. New Engl J Med 285: 938, 1971	not measured		significantly reduced

involving the enzyme dopamine β hydroxylase. Using a sensitive assay procedure, Weinshilboum et al[6] have indeed demonstrated significantly reduced enzyme activity in the Riley-Day syndrome, as well as some reduction in heterozygotes.

Because we know that catecholamines are involved as neurotransmitters, these exciting findings raise the possibility for a unifying concept for the varied pathologic manifestations of this syndrome, and also raise hope of abatement through genetic counseling, genetic engineering, or some kind of pharmacologic replacement.

Inadequate Production—Zetterstrom's Syndrome:

In normal persons, urinary excretion of adrenaline and noradrenaline increases three- to five-fold following the induction of hypoglycemia by insulin.[123]

In 1959, Broberger, Jungner and Zetterstrom reported three children with idiopathic hypoglycemia who did not manifest features of sympathomimetic response, such as tachycardia, during hypoglycemia. Subsequently, these investigators showed that five of eleven children with hypoglycemia did not have an increase in urinary catecholamine excretion following insulin-induced hypoglycemia. The suggestion was made that these patients have primary adreno-medullary failure, which in turn is responsible for their hypoglycemia. Although other investigators have confirmed these findings in some children with hypoglycemia, and good therapeutic responses have been obtained with ephedrine sulfate, the syndrome as an entity remains controversial because of two observations.

First, spontaneous hypoglycemia is extremely rare in patients with total adrenalectomy who are receiving adequate steroid replacement. Second, prolonged insulin hypoglycemia has been reported to blunt sympathetic responses.[124]

While it is difficult to reconcile these divergent viewpoints, evaluation of epinephrine and norepinephrine excretion has become established in the investigation of idiopathic hypoglycemia of childhood, and the possibility of reduced or impaired catecholamine excretion remains a consideration, primarily because of the favorable therapeutic response to replacement therapy by ephedrine.

In summary, we have presented examples of excessive, disordered and possibly inadequate catecholamine metabolism in childhood. Understanding the disturbance in catecholamine metabolism has aided the ability to diagnose and treat these disorders and has provided fertile soil for further research.

Laboratory Diagnosis of Pheochromocytoma and Sympathoblastoma

VINCENT DEQUATTRO, M.D.*

The diagnosis of the neural crest tumors, pheochromocytoma and sympathoblastoma, is confirmed in the laboratory by finding increased excretion of urinary (or, in some circumstances, increased blood) catecholamines and catecholamine metabolites. The rate of total catecholamine metabolite excretion in patients with neuroblastoma, a reflection of catecholamine biosynthesis in the tumors, is often similar in magnitude to that occurring in patients with pheochromocytoma. However, the norepinephrine stored in neuroblastoma tissues is evidently completely inactivated in the tumors, since they do not reach extra tumor receptor sites to produce cardiovascular stimulation. As was discussed by Dr. Sperling, the increased urinary excretion of the catecholamine metabolites does provide a means for the preoperative diagnosis of tumor masses occurring in infants and children. Because of the features of amine storage and metabolism peculiar to neuroblastoma, there is an increased urinary excretion of dopamine and its metabolite homovanillic acid or HVA (Chart 12). Quantitation of HVA excretion is a useful means of detecting a recurrence of the tumor after operation. Increased dopamine and HVA production in patients with pheochromocytoma usually indicates that the tumor is malignant. Increased catecholamine production in patients with pheochromocytoma is also reflected by increased plasma catecholamines.

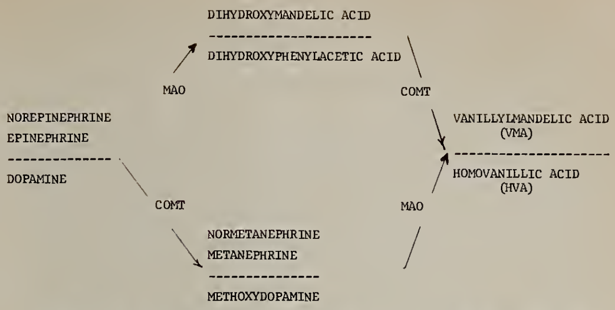

Chart 12.—Metabolic pathway for catecholamines resulting in the final products vanillylmandelic acid and homovanillic acid. The increased excretion of the catecholamines and their metabolites are shown. Those below the dash lines are characteristic of neuroblastoma and malignant pheochromocytoma. The enzymes MAO and COMT are monoamine oxidase and catechol-o-methyltransferase respectively.

Urinary Assays for Pheochromocytoma:

For screening hypertensive patients for pheochromocytoma, urine may be assayed for either total free catecholamines, total free and conjugated metanephrines and normetanephrines, or vanillylmandelic acid (VMA), depending on the preference of the particular laboratory. Most importantly, the urine should be collected during a hypertensive period or after an "attack." The catecholamines are unstable and the urine should be collected, stored and shipped to the laboratory with a preservative such as sodium bisulfite or at a pH of 3 or less. (15 ml of 6.0 N hydrochloric acid is used for a 24-hour specimen of urine.) Medications such as α methyldopa and L-Dopa are metabolized to compounds which are not separable from the endogenous catecholamines, while medications such as quinidine and tetracyclines may produce interfering fluorescence. These substances and their metabolites do not interfere with the photometric assay for VMA. Alpha-methyldopa reduces tissue norepinephrine content in patients without pheochromocytoma, causing up to a 65 percent reduction in VMA excretion. Food and beverages such as citrus fruits, coffee and chocolate have large quantities of phenolic acids which are excreted into the urine and yield a high apparent VMA. The screening kit tests for VMA in pheochromocytoma are nonspecific assays for these phenolic acids. Therefore, patients taking large quantities of food containing the phenolic acids will have false positive response to screening kit tests for VMA, which might lead to unnecessary studies and even to operation for pheochromocytoma. We have studied three patients recently at the Harbor General Hospital who had negative response to VMA screening kit tests but later were proved to have pheochromocytoma. Drugs used in the therapy of hypertension, including hydrochlorothiazide, hydralazine, reserpine, guanethidine and digitalis, do not affect the assay procedures or catecholamine metabolism enough to interfere with the diagnosis of pheochromocytoma. Further, phenoxybenzamine, phentolamine or propranolol therapy in patients with pheochromocytoma does not affect catecholamine excretion or the catecholamine assay procedures.

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In our laboratory, catecholamines[126] and metanephrines[127] are assayed by fluormetric procedures. VMA is determined by a photometric procedure.[128] We employ the assays for norepinephrine and epinephrine routinely to screen patients for pheochromocytoma when the diagnosis is either highly suspected or has been confirmed. The results of this assay help both in the localization of the tumor and in the preoperative management of the patient. A concentration of epinephrine in the urine of 20 percent or greater indicates a probable adrenal location of the tumor. A concentration of epinephrine of 30 percent or greater suggests that preoperative therapy with beta as well as alpha blockade may be required. We have measured the excretion rates of norepinephrine, epinephrine, total free and conjugated metanephrines and normetanephrines in the urine of 30 patients with pheochromocytoma (Chart 13.) Twenty-four hour urine specimens are not essential for evaluation of these patients, and in some patients it is preferable to collect timed samples during a period of hypertension and express the excretion rates of the catecholamines and their metabolites in micrograms per hour.

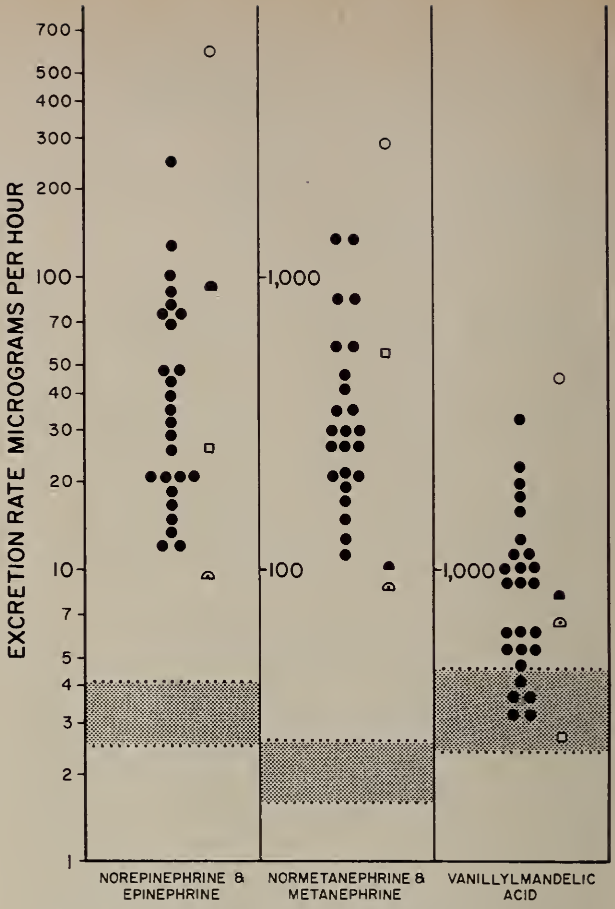

Chart 13.—Catecholamine and catecholamine metabolite excretion in 30 patients with pheochromocytoma. Twenty-three of the collections were for 24 hours, 7 were timed 2-4 hour samples. F.P. (○) was treated with guanethidine for several days prior to the urine collection. (See also Chart 14) R.Y. (□) had the lowest VMA excretion, her tumor secreted 80 percent epinephrine. T.G. (◒) a 10-year-old child, had the lowest catecholamine excretion rates. R.O. (◓) had minimal increases in normetanephrine (4-fold) and VMA (2-fold) with a 40-fold increase in catecholamine excretion. The area between the dotted horizontal lines is the mean +2 standard deviations of the mean.

The normal excretion rates expressed in micrograms per hour are as follows: total free catecholamines, 2.5 ± 0.8, 22% epinephrine; total free and conjugated metanephrines and noremetanephrines, 16 ± 5, 35% metanephrine; VMA, 240 ± 120 (values are means ± standard deviation). We have not encountered patients with pheochromocytoma who have had normal catecholamine excretion at a time during or after an "attack" of pheochromocytoma. Catecholamine excretion in excess of 10 μg per hour, metanephrine excretion greater than 60 μg per hour or VMA excretion exceeding 500 μg per hour is pheochromocytoma until proved otherwise. However, 23 percent of our patients had VMA excretion rates within the range of normal but the excretion rates of the amines were all abnormal (Chart 13). Patients with pheochromocytoma may have borderline elevations of catecholamine excretion rates in the range of 6 to 10 μg per hour. To complicate matters, there are occasional patients without pheochromocytoma who also have excretion rates of catecholamines in this range. This increased catecholamine excretion in patients without pheochromocytoma may be a result of congestive heart failure, recent surgical procedures, or various forms of non-specified stress causing excessive sympathetic nerve stimulation.[129] Usually catecholamine excretion is in the 6 to 10 μg per hour range and metanephrine excretion rates are two- or three-fold normal, whereas VMA excretion is only slightly elevated or normal in these patients. Dividing the 24-hour urine collection into day and night specimens is useful in that in patients with pheochromocytoma, the supine position at night usually does not decrease catecholamine excretion whereas during the day the upright position may

TABLE 13.—*Plasma Catecholamines in Pheochromocytoma: Before, During and After Operation*

Patient	*Norepinephrine* *Nanograms per liter*	*Epinephrine* *Nanograms per liter*
Normotensive Preoperative	530	374
Hypertensive Time of Tumor Removal	34,900	22,800
30 Minutes After Tumor Removal	1,210	861
Normotensive Subjects (25) Means ± SE	201 ± 13	82 ± 7

do so. Histamine provocative tests in three patients established that their pressor responses were associated with increases in the plasma catecholamines and catecholamine excretion rates.

Plasma Catecholamines in Pheochromocytoma:

The total plasma-catecholamines as determined by a sensitive enzymatic method[130] in normotensive subjects are in the range of 300 to 500 nanograms per liter. An infusion of norepinephrine, sufficient to raise these values to 2,000 to 3,000 nanograms per liter, will raise blood pressure levels to 190/120 mm of mercury. It is remarkable that patients with pheochromocytoma can survive with plasma catecholamines ten to fifty times this level (Table 13). However, some patients with pheochromocytoma have catecholamine elevations which are only 50 to 100 percent above normal and their values overlap with those of patients in various stressful states. The plasma catecholamine assays are more costly and not used routinely for the diagnosis of pheochromocytoma, but they may be helpful in localization.

For localization of the tumor(s), blood is taken by femoral vein catheterization from at least four sites in the vena cava—above the diaphragm, adjacent to the right adrenal gland, at the renal veins, and at the bifurcation of the vena cava. Assay of adrenal vein blood before venography is also helpful. In all of 13 patients with pheochromocytoma tested, norepinephrine and epinephrine assays of blood specimens from these locations yielded the gradations of concentrations of catecholamines required for localization of the tumors before operation. A second attempt at localization was required in two patients, since secretion of catecholamines was not occurring at the time of the first catheterization. A third patient was stimulated with histamine at the time of initial catheterization because the blood pressure was normal. The increase in plasma catecholamines localized the tumor. The plasma catecholamines were highest in the right adrenal region (right adrenal tumor) in seven patients, in the renal or left adrenal veins (left adrenal tumor) in two, and low vena cava (bladder) in one. Bilateral adrenal tumors were localized in three patients and no tumors were missed by this technique.

In one of our studies, we attempted to localize the tumor in a patient with elevated catecholamine excretion and paroxysms of hypertension, chest pain, dyspnea, sweating and attacks of a sense of impending doom associated with ventricular dysrhythmias. We performed vena cava catheterization while the patient was normotensive and attempted to stimulate the tumor with histamine in 20, 40 and 80 μg intravenous boluses without producing much increase in blood pressure or plasma-catecholamines. There was no gradient of catecholamine concentration in the blood taken from the various sites in the vena cava and the adrenal veins. On a subsequent admission for repeat catheterization during the time of a spontaneous "attack," we discovered that the patient was inducing "attacks" by self-administration of isoproterenol. Concurrent with isoproterenol, the patient self-administered furosemide and aspirin compound orally and xylocaine parenterally. It is of interest that the catecholamine excretion immediately after the "attack" was mainly that of "apparent" norepinephrine, but after several hours with excretion rates still in the high normal range, the "apparent" epinephrine concentration was from 25 to 40 percent.

There are two additional substances which have diagnostic application in families with medullary thyroid carcinoma and bilateral pheochromocytoma. High plasma concentrations of calcitonin are evidence of the medullary thyroid carcinoma[131] and metastasis may be detected by finding increased plasma concentrations of histaminase or diamine oxidase.[132]

In conclusion, the measurement of the urinary excretion of the free catecholamines during a period of hypertension, or during and after an "attack," remains the most reliable test for the diagnosis of pheochromocytoma.

Treatment of Pheochromocytoma–

Diagnosis and Preparation for Operation

VINCENT DEQUATTRO, M.D.

Localization of the Tumor(s).

Localization of the tumor(s) in a patient with pheochromocytoma may provide a valuable service to the surgeon by decreasing the operating time and the incidence of cardiovascular accident, averting unnecessary adrenalectomy, or locating otherwise hidden tumors. The history of "attacks" occurring when bending to one side, wearing a tight girdle, or when the bladder is full, may help to localize the tumors. Careful quadrant by quadrant abdominal massage (with intravenous phentolamine available) is a useful localizing technique in 10 to 20 percent of patients with pheochromocytoma. Not unusually, the diagnosis of pheochromocytoma is suggested by the finding of a suprarenal mass on an intravenous pyelogram. The pyelogram with nephrotomogram localizes the tumors in at least 60 to 70 percent of patients with proved pheochromocytoma. When these x-ray studies do not show the site, some investigators would advise no further attempt at localization because 95 percent of these tumors occur within the abdomen[66] and 85 to 90 percent occur in the vicinity of the adrenal glands. In our experience, vena cava sampling of blood for catecholamines locates tumors even when the intravenous pyelogram is negative. We advise that patients with negative pyelograms have catheterization for purposes of obtaining blood specimens from the vena cava and, if possible, the adrenal veins. Adrenal venography may be performed at this time, but the blood specimens must be obtained before the rapid injection of contrast media. We have encountered no special problems infusing contrast media into or near the site of tumors in patients with pheochromocytoma. These tumors are usually 3 to 4 cm or more in diameter, and when present in the adrenal gland, distort the adrenal venous system and become apparent on adrenal venograms. Catheterization of the left adrenal vein is usually done with ease, but that of the right adrenal veins is often not done because of technical difficulty. Some investigators prefer angiography for localizing tumors when the intravenous pyelogram is negative. Angiography may be performed as a substitute for vena cava sampling and adrenal venography—but only after adequate blocking therapy, for fatalities have occurred in unprepared patients. The procedure of retroperitoneal CO_2 insufflation, in combination with an intravenous pyelogram and nephrotomogram, often localizes suprarenal masses. However, preoperative preparation is advised for this procedure as well. A recent report describes localizing both cortical and medullary tumors in the adrenal by use of a scintiscanning technique after administration of radioactive substrates which are distributed to and concentrated in the adrenal glands.[133] The sites of occurrence and the incidence of pheochromocytomas are shown in Figure 2.

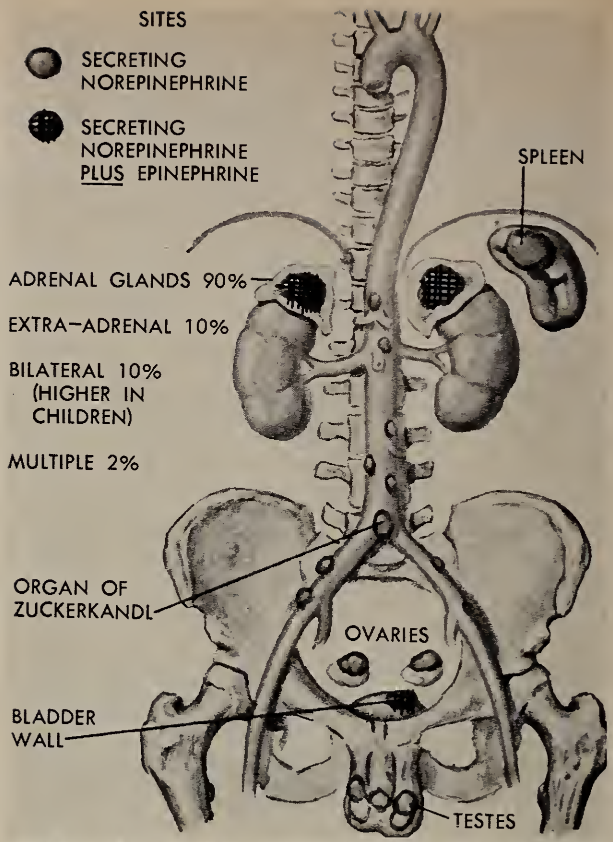

Figure 2.—Sites and frequency of occurrence of pheochromocytoma. Adrenal tumors may produce exclusively norepinephrine, exclusively epinephrine or mixtures of both.

Patients with coincident thyroid carcinoma or mucosal neuronomata have bilateral adrenal tumors. Bilateral adrenalectomy is indicated in these patients. The surgeon's fingers are the last resort in the localization of the pheochromocytoma, despite the findings of various diagnostic tests. After the known tumors are removed, a thorough exploration and manipulation of the sympathetic chain along the aorta and in the adrenal areas must be made before the surgical procedure is complete.

Pre-Operative Drug Therapy:

Specific blocking therapy should not be delayed in patients with pheochromocytoma while studies to localize the tumor(s) are under way. An exception is the patient with intermittent secretion having a vena cava study. In that case blood can be obtained after interrupting therapy during a spontaneous or induced attack of pheochromocytoma. The choice of blocking agents for therapy is dictated by the type of catecholamine secretion from the tumor. In most patients, norepinephrine accounts for 85 to 90 percent of the total catecholamine production. The alpha blocking agent phenoxybenzamine will control the hypertension and normalize blood volume of patients in this group. When epinephrine accounts for 30 percent or more of the total catecholamines secreted by the tumor, the beta blocking agent propranolol may be required in addition to phenoxybenzamine to control tachycardia and postural hypotension.

Phenoxybenzamine, the mainstay in the medical management of pheochromocytoma, is superior to oral phentolamine because it may be given once daily and it produces tachycardia and postural hypotension less frequently. Phenoxybenzamine is given once daily at the initial dose of 20 mg and increased 10 mg daily until blood pressure control is obtained and maintained for seven to ten days. Some patients have episodic attacks of hypertension and uncontrolled postural hypotension despite careful adjustment of dosage with these agents. Physical activity may have to be restricted and perhaps total bedrest will be required in an occasional patient before corrective operation is carried out. The cardiomyopathy related to catecholamine hypersecretion and described as a myocarditis has responded to alpha blocking therapy in patients with norepinephrine-producing tumors.[134] Patients with myocardiopathy, recent myocardial infarction, or stroke should be treated medically for several months until they have recovered from these complications.

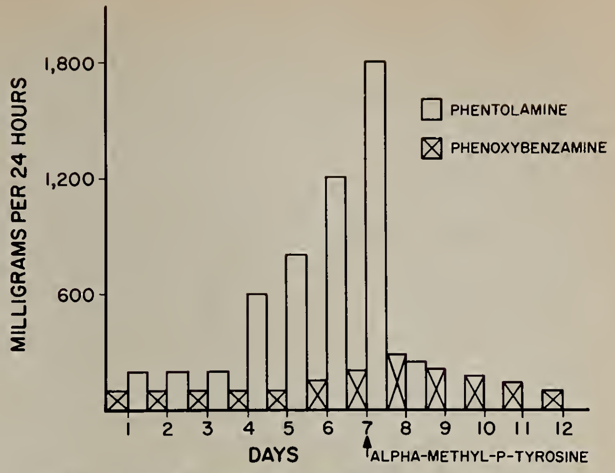

Chart 14.—Reduced requirement of alpha-blocking therapy after administration of α-methyltyrosine in a patient with pheochromocytoma. One mg of phentolamine costs $1.00.

The beta blocking agents, introduced clinically in the 1960's, further improve the preoperative management of patients with pheochromocytoma. Pronethalol, related to the prototype compound dichloro-isoproterenol, caused neoplasms in laboratory animals, but the subsequent introduction of propranolol has provided a useful and safer means for beta blockade. Patients with pheochromocytoma are sensitive to as little as 10 mg of propranolol daily. The drug should be started after phenoxybenzamine therapy has been instituted, since in some patients propranolol reverses the hypotensive effects of epinephrine into hypertensive responses. Low dosages of propranolol are all that are usually required for the control of tachycardia in patients with pheochromocytoma.

Occasionally a highly unusual patient may be seen. Here at Harbor Hospital, a patient with a tumor secreting large quantities of both norepinephrine and epinephrine was treated with more than 1,000 mg of phentolamine and hundreds of milligrams of phenoxybenzamine and propranolol per day without blood pressure control. The introduction of the biosynthetic blocking agent α-methyltyrosine achieved adequate blood pressure control within 24 to 36 hours. The resulting diminution in requirement of phenoxybenzamine and phentolamine after methyltyrosine is shown in Chart 14. Methyltyrosine, a competitive inhibitor of tyrosine hydroxylase, the first step in norepinephrine biosynthesis, is effective in short and long-term management of pheochromocytoma.[66] However, long-term therapy with methyltyrosine has produced symptoms of parkinsonism.[135]

Medical Management in the Operating Room:

Both alpha and beta blocking agents have special value in the operating room during the removal of the pheochromocytoma. Despite excellent preoperative control, including the administration of the oral blocking agents until the time of operation and the prophylactic administration of phentolamine intravenously just before anesthesia, large quantities of catecholamines secreted by the tumor during the induction of anesthesia and the surgical manipulation may require frequent intravenous boluses of phentolamine. These are administered in 5 mg amounts as often as necessary to lower blood pressure to safe levels. Larger amounts of phentolamine can be administered by constant intravenous infusion of a solution delivering 0.5 to 1.0 mg per minute. To detect the momentary fluctuations in blood pressure, arterial monitoring by transducer strain gauge recording is required. Reliance on blood pressure recording via sphygmomanometer is hazardous since large fluctuations in intra-aortic pressure may not be detected by the indirect brachial artery pressure measurements. Supraventricular tachycardia occurs frequently in association with hypertensive episodes during operation, and it responds to the rapid administration of intravenous phentolamine. Arrhythmia of this type usually requires no other medication.

Much has been said about the use of the anesthetic halothane in patients with pheochromocytoma.[66,136] Although halothane has a suppressive effect on the cardiovascular system, it sensitizes the myocardium to the arrhythmogenic properties of epinephrine and norepinephrine. We have not encountered ventricular dysrhythmias, either multiple premature ventricular contractions, ventricular tachycardia, or fibrillation in patients who have had anesthesia without halogenated hydrocarbons. The anesthetic agents used in the majority of our patients were nitrous oxide, pentothal, meperidine and fentamyl. Investigators proposing halothane as the anesthetic agent of choice in pheochromocytoma have also described numerous ventricular dysrhythmias in their patients.[66] Ventricular dysrhythmias usually respond to 2 to 5 mg boluses of propranolol intravenously. When propranolol is not successful, lidocaine in 50 to 100 mg boluses is used to convert the ventricular dysrhythmia to normal sinus rhythm.

It is of utmost importance that the surgeon clamp the veins draining the tumor and the involved adrenal gland before extensive handling of the tumor to avoid expressing the catecholamines into the circulation. After the tumor has been removed, there is usually an immediate fall in blood pressure to normotensive or hypotensive levels (Table 13). The central venous pressure then becomes a major guide for postoperative management. Immediately after removal of the tumors, blood or plasma expanders are administered rapidly to over-replace blood loss until venous pressure is normal or slightly increased. With this technique, the pressor agents are required only rarely. Occasionally, there are minor fluctuations in blood pressure for 24 to 48 hours and the arterial line is usually left in place until the morning after operation. If the patient has had total adrenalectomy, 100 mg of hydrocortisone is given intravenously at that time and every eight hours, with a subsequent gradual tapering to a maintenance dosage of oral cortisone over a period of six or seven days.

Pheochromocytoma is a spectacular disorder, and successful therapy requires a team approach. The diagnosis should include knowledge of the secretory products of the tumors, the localization of the tumors, the careful preoperative normalization of the blood pressure depending on these findings, and the surgical removal of the tumor under a controlled physiological state made possible by the avoidance of halogenated hydrocarbons and utilization of direct arterial pressure and central venous pressure monitoring devices. Finally, "excessive" amounts of blood or plasma-expanding agents may be required after the tumor is removed.

Questions and Answers

Dr. Odell: Thank you very much, Dr. DeQuattro. The speakers will now attempt to answer any questions the audience may have. While the audience is thinking, I'd like to ask a few questions. I would like to ask Dr. Lubran (Director of Clinical Laboratories) the first one. We have had a problem, for some time, with the screening procedure for catecholamines here at Harbor Hospital, as Dr. DeQuattro has stated. The last three patients with pheochromocytoma at Harbor Hospital *proved* at operation, had negative screening tests. Would you be willing to comment on the procedure that is being used now at our institution? What screening laboratory test might we have done in our hospital now for patients we suspect having a pheochromocytoma?

Dr. Lubran: The previous screening test which we used depended on colorimetric reactions, as Dr. DeQuattro pointed out, and was really detecting *phenolic* substances. A subtle color change is rather difficult to detect, and to be able to distinguish small increases from normal baselines is difficult. We are trying to sharpen the method now so that the test is much easier to carry out. In fact, we are developing a semi-quantitative method for VMA which depends on the spectrophotometric reading rather than on the visual interpretation.

Dr. Odell: Dr. DeQuattro, you showed that the *total* VMA *excretion was normal in* several of your patients with pheochromocytoma. Would you be willing to state what we should use optimally to screen patients with sustained hypertension, in routine evaluation of the cause? What should we use to rule out the possibility of pheochromocytoma?

Dr. DeQuattro: Well, I think you should use what we use—that is, the measurement of the *total* catecholamines. I don't think it would be necessary for you to routinely quantify norepinephrine and epinephrine as a screening procedure. However, some investigators would advocate using metanephrines, because you can measure the two—the normetanephrine and metanephrine—and there is less likelihood of missing the diagnosis of pheochromocytoma than with total VMA's. As far as expense is concerned, total VMA is the least expensive of all these assays, but I don't think cost alone should be a good reason to limit screening to this assay. In summary, then, the answer would be: Measure total urinary catecholamines. When your index of suspicion is high, you must also quantify the epinephrine and norepinephrine separately.

Dr. Odell: Thank you, Dr. DeQuattro. I might now ask a question of Dr. Sperling. He has just discussed Zetterstrom's syndrome and used the fact that patients with bilateral adrenalectomy do not suffer from hypoglycemia as some evidence that this was not a deficiency of catecholamine secretion. However, if I recall correctly, after bilateral adrenalectomy of an adult, the urinary catecholamine excretion falls only transiently and then returns to nearly normal levels. The source of the catecholamines in such patients is the sympathetic nerve endings and these patients do not suffer from hypoglycemia. However, if a total defect in synthesis existed in both sympathetic nerve endings *and* in the adrenal medulla, perhaps hypoglycemia might result. The fact that bilateral adrenalectomy does not cause hypoglycemia might not be an argument at all against the thesis that Zetterstrom's syndrome is a disease caused by a defect in catecholamine synthesis of *both* adrenal and nerve endings.

Dr. Sperling: I knew you would ask, but we still have to explain the hypoglycemia that one sees in children on the basis of adrenal deficiency or catecholamine synthesis. There is no reason to suppose that children do not recover this ability to excrete catecholamines in urine from the sympathetic nerve endings, ganglia, etc. So what I tried to raise was the question whether deficiency of the catecholamines released by the adrenal medulla itself is responsible for a specific syndrome.

Dr. Odell: Do the children with Zetterstrom's syndrome recover spontaneously with age?

Dr. Sperling: They tend to get better with age.

Dr. Odell: One last question and then perhaps some of you will have other questions. Dr. DeQuattro showed the striking response of our patient to alpha methylparatyrosine. I would like to ask Dr. DeQuattro why isn't this the best routine preoperative management of all patients with pheochromocytoma?

Dr. DeQuattro: Some side effects occur. Central nervous system symptoms mimicking parkinsonism have been observed when the drug has been used for several months in treatment of malignant pheochromocytomas. These symptoms may not be reversible. Dr. Inglesman assures me, based on his several years' experience with this drug, that over short-term periods of weeks this is an excellent drug—and without side effects. However, over a longer period, these problems, which I think may be related to dopamine metabolism just like the deficiency described in parkinsonism, have been observed. There was one remark by one investigator that the drug-induced tremor responded to dihydramine just as the tremor of parkinsonism sometimes does.

Dr. Odell: Are there any other questions of the speakers?

Dr. Calescibetta: I would like to ask Dr. DeQuattro: Have you ever seen any patients with pheochromocytoma and significantly compromised renal function? If so, did renal function return to normal after removal of the tumor?

Dr. DeQuattro: No, I haven't but anything is possible. We have been caring for a patient with pheochromocytoma who had grade four retinopathy and severe papilledema with loss of vision and wide swinging blood pressure, but who had a normal blood urea nitrogen. In view of the retinopathy I am perplexed at the normal BUN. We have shown that she does have pheochromocytoma. Nephrotic syndrome has been reported in association with pheochromocytoma, but I am not aware that increases in BUN or creatinine occur.

Dr. Odell: I'll ask Dr. DeQuattro one more question. Dr. Swerdloff has reviewed the blood volume data that Dr. Waldmann reported in pheochromocytoma patients. These were striking in that almost all were within normal range. Yet it is all of our experience, and you restated this, that preoperative hyperexpansion of the plasma volume is very useful in preventing complications during operation. Do you think that these two statements are incompatible? Is it not possible, in fact, that these are patients with normal blood volume who have lost ability to control their blood pressure at the precapillary-sphincter or arteriolar level, and if you hyperexpand them above normal, you are preventing *hypo*tension. If we measure blood volume after treatment, they might indeed be above normal. Is this a likely explanation, rather than that blood volume is actually below normal and that these data are in error?

Dr. DeQuattro: I think there are several aspects of this controversy. One is the number of patients studied. Dr. Waldmann has studied 12 or 13 patients and four of them were clearly below normal—two standard deviations below normal. Thus even in his series, 25 percent had low blood volumes. Brunjes et al studied three patients ("Pheochromocytoma: Post Operative Shock and Blood Volume," by Shannon Brunjes, Varner J. Johns, Jr., and Milton G. Crane, New England Journal of Medicine 262: 393-396, February 25, 1960) and, all three had decreased blood volume. That's a 100 percent incidence of reduced blood volume.

Another aspect might be discussed: What does one actually measure when blood volume is quantified? Whether you use the RISA or the labeled chromium technique, you must utilize the venous hematocrit for calculation. The venous hematocrit reflects the proportion of red cells to plasma in the large vessel, the vein. What is the proportion in the small constricted blood vessels distally? There is some evidence to show that skimming of red cells occurs so that the red cell actually is preferentially shunted. In many patients (the last patient I talked about, who had malignant hypertension, is an example) one sees an increased hematocrit. Does this mean that such a patient has a deficiency in plasma volume centrally and not peripherally? I do not know the answer to that. However, I think that the different published reports are not incompatible when these unknowns are kept in mind. I think when we know actual capillary hematocrit and then calculate a true blood volume, we may find the answers to these questions.

Dr. Jerald Bain (Research Fellow, Division of Endocrinology, Harbor Hospital): Will the precatecholamines or metanephrine always be elevated regardless of whether the patient is in a paroxysm or not?

Dr. DeQuattro: No. Sometimes in paroxysm-producing tumors, excretion will return completely to normal. On the other hand, some patients with greatly fluctuating secretion of cathecholamines will have normal blood pressures. The only thing you can count on is that if you obtain the urine or the blood specimen when the patient is *hypertensive,* you will find the elevation.

Dr. Andrew Soll (Medical Resident): I was wondering, Dr. DeQuattro, what the reason was for using propranolol alone for treatment of pure epinephrine secreting pheochromocytoma tumors in patients with cardiac arrhythmias? Doesn't this increase the risk of a hypertensive crisis by blocking only the beta receptors, leaving the alpha receptor effect uncontrolled?

Dr. DeQuattro: I would like to restate what I said about the pure epinephrine producing tumors. In all of our patients, our mainstay of therapy is phenoxybenzamine, an alpha blocking agent. This drug is used because, as you noted *epinephrine has both alpha and beta stimulating effects.* We don't want to modify the effects of epinephrine into purely alpha stimulating which might result in severe hypertensive response. Indeed, there is a test that has been advocated as a provocative test for pheochromocytoma: propranolol is administered and in patients with pheochromocytoma, blood pressure increases. In each patient that we treat, we start with phenoxybenzamine and then add propranolol, whether they have exclusively epinephrine or partially epinephrine secreting tumors.

Dr. Odell: I would like to thank each of the speakers and also the audience for coming today.

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IN EVALUATING ABDOMINAL INJURY, ASK WHAT HAS BEEN DONE THUS FAR

In evaluating the patient with abdominal injury, it's important to find out whether he has had any previous medical treatment. In many instances patients are seen in one emergency room and referred to another. I would like to warn against three bad practices. One is the injudicious use of narcotics in the patient with a potential intra-abdominal injury. One of the things that we look for and use to follow this patient and to diagnose the nonobvious intra-abdominal injury is the presence of pain. The patient who has just had 150 milligrams of Demerol® or a large slug of morphine presents many problems that may well result in a delay in diagnosis, a delay in definitive treatment, and the death of the patient.

Something else we need to know is the history of fluids. Has the patient had a lot of intravenous fluids? Has he had 500 cc of water, which is not proper treatment for a patient in shock, or 10 liters of lactated Ringer's solution during transfer or transport into the hospital? These are the two extremes. But this knowledge can be very helpful in evaluating the status of the patient, particularly if you are looking for hidden intra-abdominal bleeding and you are worried whether the patient really has the bleeding. How much resuscitation has he had? Get this information—it's very necessary.

Finally many of us injudiciously give antibiotics which will mask a perforated viscus or intestine, particularly in the patient seen late.

—Max S. Rittenbury, m.d., Charleston, S.C.
Extracted from *Audio-Digest Surgery,* Vol. 18, No. 16, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Refer to: Clinical spectrum of Sjögren's syndrome—Medical Staff Conference, University of California, San Francisco. Calif Med 117:63-69, Sep 1972

MEDICAL STAFF CONFERENCE

The Clinical Spectrum of Sjögren's Syndrome

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

Dr. Smith:* Mikulicz first described the pathological changes in the salivary and lacrimal glands and the associated clinical manifestations. In the following years there were other contributions relating to this interesting syndrome. These contributions were culminated in the excellent clinical work of the Swedish ophthalmologist, Henrich Sjögren, in the 1930's. It is part of the injustice of medical history that this syndrome has become known as Sjögren's syndrome, and Mikulicz's syndrome has been somewhat submerged. The Medical Staff Conference today will be devoted to a consideration of this interesting disorder. The case history will be given by Dr. Watts.

Dr. Watts:† The patient is a 68-year-old caucasian woman who presented with the chief complaint of dry eyes and mouth. Her present illness began two years before admission when pruritus developed in association with increasing dryness and redness of the skin. The dryness of mouth caused some interference with speech and swallowing, and the patient noted a grainy sensation and dryness of her eyes. Dryness and pruritus of the vaginal mucosa were also prominent complaints. The patient also fatigued easily and experienced an increase in dental caries over the same period of time. The patient's past medical history was unremarkable except for a possible allergic sensitivity to penicillin. On physical examination the patient's blood pressure was 160/90 mm of mercury, pulse 100 beats per minute, and respirations 18 per minute. The skin was dry and scaly, the parotid glands slightly enlarged but not tender. The Schirmer test showed 10 mm of bilateral wetting. No abnormalities were noted on examination of the heart, lungs and abdomen, and there were no pathologic changes in the joints. The erythrocyte sedimentation rate was 36 mm in one hour. Leukocytes numbered 3,000 per cu mm with 52 percent polymorpholeukocytes. The blood sugar was normal, and the serum uric acid was 8.9 mg per 100 ml. Serum protein electrophoresis showed a slightly elevated gamma globulin fraction, and there was a positive antinuclear antibody with a speckled pattern. The rheumatoid factor was positive at a 1 to 3,200 titer. An x-ray film of the chest and electrocardiogram were within normal limits.

During the stay in hospital, salivary scintigraphy with 99m technetium showed a decreased accumulation in the parotid glands. There was only transient uptake in the submandibular glands, and there was no accumulation of the label in the mouth during the course of the study. The findings were interpreted as very abnormal. A sialogram was normal on the right side and abnormal on the left. A lip biopsy revealed increased infiltration of plasma cells and lymphocytes, as well as hyperplasia of the epithelial cells of the salivary ducts. Thickening of the walls of the salivary ducts and a moderate increase of connective tissue throughout the stroma were also observed. These findings were consistent with the diagnosis of Sjögren's syndrome.

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*Lloyd H. Smith, Jr., M.D., Professor and Chairman, Department of Medicine.

†David Watts, M.D., Resident in Medicine.

Dr. Smith: We are pleased to have Dr. Martin Shearn to discuss this case. Dr. Shearn has had a long time interest in this syndrome and has recently published a superb monograph on this topic.

Dr. Martin A. Shearn:* Thank you, Dr. Smith. Perhaps we can define Sjögren's syndrome as a chronic inflammatory disorder, characterized by dryness of the mouth, eyes, and other mucous membranes, and frequently associated with a rheumatic disease. Today's patient illustrates a number of the clinical characteristics of Sjögren's syndrome. She presented with dryness of the eyes, mouth, and vagina. She had the typical serological reactivity so often seen in Sjögren's syndrome, manifested by hypergammaglobulinemia and positive reactions to tests for antinuclear antibody and rheumatoid factor. Confirmatory evidence for the diagnosis is offered by the characteristic histopathology in her minor salivary glands.

Ocular Tests

Although Sjögren's syndrome is a systemic disorder, the diagnosis may most often be established by directing attention to the eyes and salivary glands. The anterior surface of the normal eye is protected by a tear film made up largely of lacrimal secretions. In Sjögren's syndrome there is atrophy of the secretory epithelium of both the major and the minor lacrimal glands, leading to desiccation of the cornea and conjunctiva (keratoconjunctivitis sicca). In advanced cases, the cornea may undergo severe damage; in such instances, epithelial strands are seen hanging down from the corneal surface (keratitis filiformis), in association with degeneration of the conjunctival epithelium. This late result may be prevented by the use of artificial tears which indicates the importance of early diagnosis.

The ocular test most widely used for diagnosis is the Schirmer test: filter paper strips placed under the eyelids at the inner canthus measure the quantity of tears secreted in 5 minutes in response to irritation. A normal young person usually wets 15 mm or more of the paper strip. Since hypolacrimation accompanies age, about one-third of presumably normal elderly persons may wet only 10 mm of the paper in 5 minutes. When wetting of 5 mm or less is employed as the cut-off point, about 15 percent of normal persons and patients with Sjögren's syndrome are misclassified.[1] This, then, is a crude test which is of limited value and may not be sensitive or specific enough for our usual clinical purposes. Since better tests are available, our attention should be directed to them. The relative merit of the various ocular diagnostic techniques has recently been reviewed.[2]

A simple and useful technique for the diagnosis of Sjögren's syndrome is measurement of tear lysozyme concentration by electrophoresis or by determining the diameter of lysis on agar plates impregnated with M. lysodeikticus. So tested, lysozyme concentration is found to be low in tears of patients with keratoconjunctivitis sicca and tends to vary with the severity of the disease. The test is highly reliable and yields excellent separation of normal subjects from patients with Sjögren's syndrome.

The characteristic signs of keratoconjunctivitis sicca are best evoked by ocular staining techniques. One of the most useful and widely employed materials for such staining is rose bengal, a fluorescein derivative. When a drop of rose bengal solution is instilled into the eye of a patient with Sjögren's syndrome, that portion of the eye which fills the palpebral aperture takes up the dye. In the fully developed disease, red triangles with their base toward the limbus are seen. The cornea, especially in its lower portion, is also stained (Figure 1). Such findings are pathognomonic of Sjögren's syndrome.

Salivary Gland Abnormalities

One of the major characteristics of Sjögren's syndrome is parotid enlargement. Approximately 25 to 50 percent of patients with Sjögren's syndrome present with enlargement of one or more parotid or submandibular glands. Salivary gland enlargement may occur in certain other diseases, such as hyperlipoproteinemia, malnutrition, cirrhosis of the liver, and diabetes mellitus. In such conditions, the glands tend to feel soft and puffy, and the mouth and eyes are not usually dry. The

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*Martin A. Shearn, M.D., Associate Clinical Professor of Medicine, University of California San Francisco, and Director of Medical Education, Kaiser Foundation Hospital Oakland.

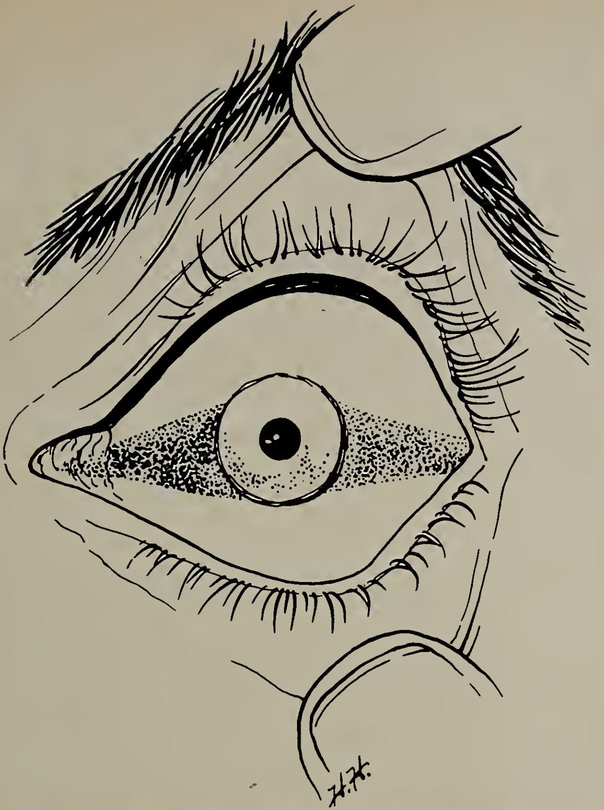

Figure 1.—Appearance of the eyes with rose bengal solution in keratoconjunctivitis sicca.

clinical setting in which the salivary enlargement occurs should help to suggest the diagnosis.

When the salivary glands become atrophic, saliva becomes deficient in quantity and is qualitatively altered, resulting in xerostomia. The mouth becomes exceedingly dry and the lips and oral mucous membranes become atrophic. The patient has difficulty in speaking, swallowing, and eating. Other effects of salivary gland atrophy are anosmia and rampant dental caries. Apparently saliva is necessary for healthy dentition. Its importance was demonstrated in a study in which the number of caries that developed in hamsters fed a cariogenic diet and simultaneously desalivated was ten times the number that occurred in those on the diet alone.[3]

A number of procedures have been employed to assess salivary gland function, including measurements of salivary flow, sialography, and salivary scintiscan. Sialography is a worthwhile adjunct to diagnosis, since the sialographic pattern is often abnormal even when the salivary glands are not clinically enlarged. It tends to correlate well with the degree of abnormality in the gland and with the severity of xerostomia. The procedure, however, may cause pain and swelling of the gland and there may be extravasation of the dye, which further disturbs glandular function. Allergic responses to contrast media have been recorded.

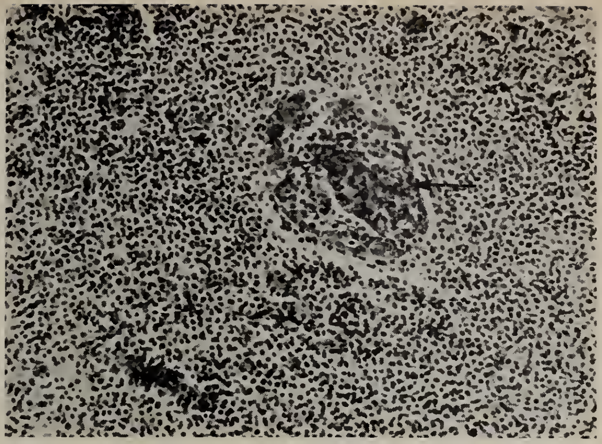

Figure 2.—Parotid biopsy specimen from patient with Sjögren's syndrome showing epimyoepithelial island (arrow) and intense lymphocytic infiltration.

An extremely promising new technique for salivary gland evaluation is scanning with the radioactive element 99m technetium (^{99m}Tc). Normal salivary gland concentrates ^{99m}Tc, producing a bright image on the scintiscan; the diseased gland fails to concentrate this material appropriately.[4] Sequential salivary scintigraphy yields curves of the uptake and excretion of ^{99m}Tc by salivary glands. In the normal gland there is rapid uptake, peaking at about a half-hour; radioactivity appears in the oral cavity in approximately 10 minutes. In patients with Sjögren's syndrome the curve usually fails to peak within an hour, and the oral cavity often shows no evidence of radioactivity throughout the study. This test is simple, free of side effects and non-invasive. It appears to be of special use in monitoring changes in salivary gland function induced by therapeutic maneuvers or that occur during the course of disease.

Confirmation of Sjögren's syndrome may be obtained by salivary gland biopsy. The pathological picture, apparently unique to this disease, has two basic features: massive lymphoid infiltration with atrophy of the acinar tissue, and ductal alterations characterized by intraductal cellular proliferation leading to narrowing of the lumen and eventually to the formation of compact cellu-

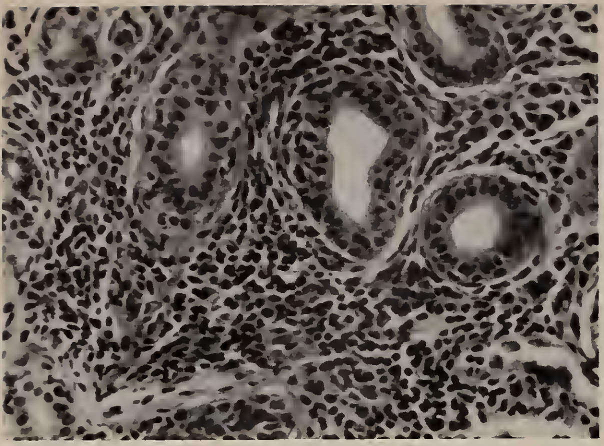

Figure 3.—Biopsy specimen of labial mucosa from a patient with Sjögren's syndrome showing intraductal cellular proliferation and lymphocytic infiltration.

lar structures which have been termed epimyoepithelial islands[5] (Figure 2).

Since the minor salivary glands are also involved in the general polyglandular abnormality of Sjögren's syndrome, recent attention has focused on the labial glands as a convenient source of biopsy material. These are easily accessible; the biopsy procedure leaves no noticeable scar, and has few objectionable side effects. The histological abnormality of Sjögren's syndrome in the labial glands is similar to that in the major salivary glands, and permits diagnosis (Figure 3). This procedure, however, does not necessarily supplant parotid biopsy, which may still be required for patients who present with unilateral parotid swelling or other features that pose a diagnostic problem.

Associated Connective Tissue Diseases

One reason that Sjögren's syndrome has been of great interest to medicine is its frequent association with other disease. As Chart 1 shows, Sjögren's syndrome may be found in association with rheumatoid arthritis, scleroderma, lupus erythematosus, polymyositis, chronic hepatitis, Hashimoto's thyroiditis, pulmonary fibrosis, or lymphoproliferative neoplastic disorders. All have in common certain autoimmune characteristics; and in each, lymphocytic infiltration may involve certain major structures. Of the various disease states that may be found in association with Sjögren's syndrome, rheumatoid arthritis is most common. The criteria for its diagnosis are present in approximately 30 to 50 percent of patients with Sjögren's syndrome,[6,7] and if patients with rheumatoid arthritis are appropriately studied for the presence of Sjögren's syndrome, a significant minority will prove to have this disorder. Ocular screening by rose bengal in patients with rheumatoid arthritis has revealed keratoconjunctivitis sicca in 10 to 15 percent, while in one study 34 percent of those with advanced rheumatoid arthritis had this ocular complication.[8] If one were to subject these patients to further diagnostic study, utilizing for example lip biopsy or salivary scintiscan, it is estimated that a quarter of them might be found to have Sjögren's syndrome.

Systemic Manifestations

Not only hypofunction of the salivary and lacrimal glands, but also dryness of the pharynx, trachea, nasal mucosa, bronchi, vagina, and skin are features of Sjögren's syndrome. Sjögren's syndrome also affects a variety of other tissues and organs. Of the systemic manifestations, the renal are among the most interesting. Renal tubular acidosis presenting as hyperchloremic acidosis may occur in approximately 20 percent of patients with Sjögren's syndrome. The defect in renal acidification is usually of Type I (classic, gradient, or distal). Such a defect is related to the inability of the distal nephron to overcome a steep hydrogen ion concentration gradient. Several cases of Sjögren's syndrome in association with physiological dysfunction of the proximal tubule have also been reported. In one of these cases, aminoaciduria, phosphaturia, uricosuria, and nephrogenic diabetes insipidus were present.[2] Renal tubular acidosis of a subclinical or incomplete form, lacking the overt feature of hyperchloremic acidosis, has also been noted in patients with Sjögren's syndrome and to be uncovered by an ammonium chloride loading test.[9] Osteomalacia, nephrocalcinosis, and hypokalemia may all occur in association with the renal tubular acidosis of Sjögren's syndrome. Renal biopsy in patients with Sjögren's syndrome often reveals changes of chronic interstitial nephritis with lymphocytic infiltration and fibrosis of the interstitial areas, as well as periglomerular fibrosis and abnormalities of the tubules. The glomeruli are for the most part preserved. Electronmicroscopic studies have failed to show electron-dense deposits on the glomerular basement membrane.[10] Interstitial nephritis may occur at any time during

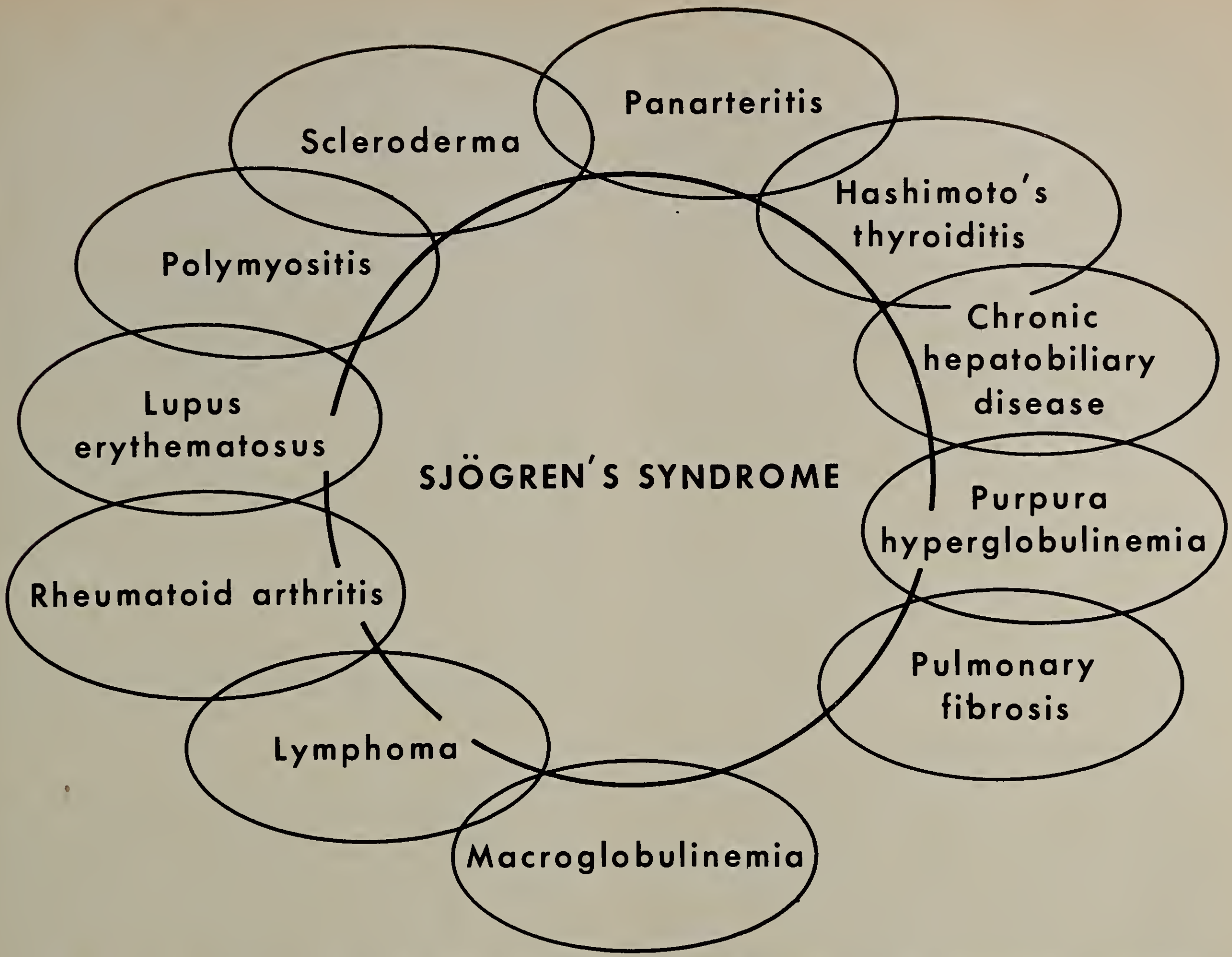

Chart 1.—The spectrum of disorders associated with Sjögren's syndrome. (From Shearn MA: Sjögren's Syndrome, Philadelphia, W. B. Saunders Co., 1971.)

the life history of the patient with Sjögren's syndrome, and in some it may progress to renal insufficiency and uremia.[2]

Although glomerulonephritis has been observed in patients with Sjögren's syndrome, it is rare, and usually associated with mixed cryoglobulinemia.[11] Why, in contrast to systemic lupus erythematosus, does Sjögren's syndrome often spare the glomerulus in spite of many clinical similarities between these two diseases? A possible explanation was provided by the demonstration of a striking absence of reactivity against deoxyribonucleic acid (DNA) in serum of patients with Sjögren's syndrome. Such reactivity is generally seen in patients with lupus erythematosus and immune complex disease.[11] Since antibodies to DNA may participate in the pathogenesis of soluble immune complex deposition, a possible explanation is thus offered for glomerular sparing in Sjögren's syndrome.

Lymphoproliferation

Another intriguing aspect of Sjögren's syndrome is the occurrence of lymphoproliferative neoplasms in an incidence far above that which could be explained by chance alone. To date some 40 or so patients have been reported to have Sjögren's syndrome and associated neoplasms, the majority being undifferentiated lymphomas. In Sjögren's syndrome there appears to be a spectrum of abnormalities ranging from lymphocytic infiltration in glandular structures, through intense lymphocytosis in organ structures, to frank lymphatic malignant neoplasia. Of 58 patients with Sjögren's syndrome in one study,[12] reticulum cell sarcoma developed in three and Waldenström's macroglobulinemia in a fourth. Other patients have been observed to have extrasalivary lymphoid abnormalities sufficiently pronounced to arouse clinical suspicion of lymphoma. In some of these cases lymph nodes contain cells of primitive appearance which obscure the glandular landmarks.

Patients with lymphoid abnormalities are considerably more likely to show generalized lymph node enlargement, salivary gland swellings, splenomegaly, purpura, vasculitis, and neuropathy than those without such abnormalities. There is a lower incidence of rheumatoid arthritis in these patients than in patients with Sjögren's syndrome in whom lymphoproliferative diseases do not develop. Of interest is the fact that malignant lymphoma is being observed in a number of other clinical settings characterized by immunological aberrations and autoimmunity.[13] Another possible parallel to Sjögren's syndrome is seen in mice that survive a graft-versus-host reaction, then succumb to malignant lymphoma. In addition, lymphoma develops with relative frequency in the New Zealand Black (NZB) mouse, which incurs a disease in many ways similar to Sjögren's syndrome.

Immunological Findings

One of the most characteristic features of Sjögren's syndrome is the remarkable immunological reactivity detected in serum. In the majority of patients with Sjögren's syndrome, the serum contains antigammaglobulin antibodies, antinuclear antibodies and gamma globulin in heightened concentrations. A gamut of other serological abnormalities, including antibodies against salivary duct, lacrimal gland, smooth muscle, mitochondria, and thyroid gland have all been noted. Rheumatoid factor has been detected in over 90 percent of cases, irrespective of the presence or absence of rheumatoid arthritis.[6] About 50 percent of patients have antibodies directed against salivary duct cells,[14] and the LE preparation is positive in some 15 to 20 percent of patients with Sjögren's syndrome. Serological abnormalities tend to occur in families of patients with Sjögren's syndrome and are seen in family members without overt evidence of disease.[2] In spite of the tendency to increased humoral antibody concentrations, cell-mediated immunity has been shown to be impaired in Sjögren's syndrome. Peripheral blood lymphocytes are functionally abnormal in their response to mitogenic agents. Patients with Sjögren's syndrome also have a decreased capacity to develop delayed hypersensitivity to a specific contact allergen.[15] Thus it seems that there is a discordance of thymus (T)cell and bone marrow (B)cell function. Since cell-mediated immunity appears to play a vital role in immunological surveillance against clones of cells with oncogenic potential, depression of this function would seem to have special meaning in a disease with increased incidence of malignant neoplasia.

Other laboratory abnormalities include elevated sedimentation rate in approximately two-thirds of the patients, anemia in one-third, and leukopenia and eosinophilia in about one-fourth.

NZB Mouse

The NZB mouse, a highly inbred New Zealand strain originally developed for cancer research, spontaneously develops autoimmune hemolytic anemia with a high incidence of positive direct Coombs tests and, less commonly, antinuclear antibodies. In the hybrid produced by crossing the NZB mouse with another inbred strain, the New Zealand White (NZW), a disease remarkably similar to systemic lupus erythematosus developed, including alopecia, skin lesions, splenomegaly, hepatomegaly, autoimmune hemolytic anemia, and immune complex nephritis. Antinuclear antibodies, positive LE preparations, and a high incidence of double-stranded DNA were found in the blood. Of special interest was observation of the characteristic histopathological features of Sjögren's syndrome in the salivary gland tissue of those animals that were studied after four months of life.[16] As the mice aged, salivary gland abnormalities increased and typical epimyoepithelial islands were seen. The cornea and conjunctiva showed changes similar in many ways to the ocular features of Sjögren's syndrome in man. These mice harbored the Gross leukemia virus; and cell-free filtrates from them, injected intraperitoneally into young adult Swiss-Webster mice, produced lymphoid cell hyperplasia, glomerlonephritis, and hypergammaglobulinemia in these animals.[17] Also of note was the development of lymphomas in approximately 10 percent of the NZB-NZW hybrids.

The possible parallels of the mouse disease to Sjögren's syndrome as it occurs in man have been most intriguing. In the mouse the interaction of genetic, immunological, and viral factors appears to account in large part for the disease process. If we were to extrapolate to man, would it be possible that in a susceptible, genetically predis-

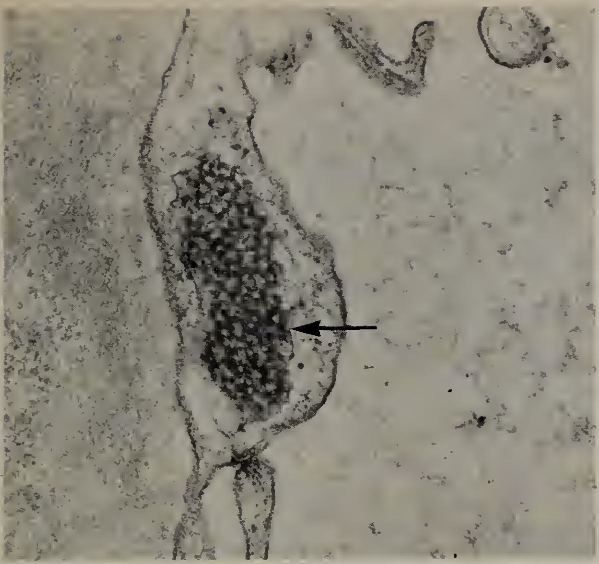

Figure 4.—Electron micrograph of renal biopsy specimen from a patient with Sjögren's syndrome showing microtubular structure (arrow) within a cytoplasm of endothelial cell. (From Shearn MA: Sjögren's Syndrome, Philadelphia, W. B. Saunders Co., 1971.)

posed individual with altered immunologic balance, a slowly acting agent such as a latent virus might produce the disease? Thus far, evidence has not been forthcoming that human Sjögren's syndrome is a viral disease. However, microtubular structures similar to those observed in systemic lupus erythematosus have now been seen in cells from several organs (Figure 4) as well as in circulating lymphocytes of patients with Sjögren's syndrome. Although much controversy surrounds the nature of these structures many investigators believe they are not actually viruses but are in some manner virus-related—perhaps the trace or evidence that a virus has been present.

The further elucidation of the responsible host and environmental factors that participate in the etiology of Sjögren's syndrome should prove important to our understanding not only of other connective tissue diseases, but also of the relation of autoimmunity to malignant neoplasia.

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HYPOPHYSECTOMY FROM ABOVE—NOT FOR DIABETICS

Doing any type of hypophysectomy from above in diabetics is bad business. About ten years ago at Memorial Hospital this procedure was done for two kinds of cases—diabetic retinopathy and metastatic breast cancer. It turned out that in the breast cancers there were never any postoperative convulsions. But in 90 percent of the diabetics there were convulsions over periods as long as five years. The vasculature is so poor in these people that by reflecting the frontal lobes and pushing them around, you create damage that leads to convulsions. This fact led many people to give up hypophysectomy from above in late-stage diabetics.

—PANEL DISCUSSION ON MANAGEMENT OF DIABETIC RETINOPATHY

Extracted from *Audio-Digest Ophthalmology,* Vol. 9, No. 13, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Important Advances in Clinical Medicine

Epitomes of Progress -- Otolaryngology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Otolaryngology. Each item in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Otolaryngology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panels to the Section on Otolaryngology of the California Medical Association and the summaries were prepared under their direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

A New Approach (Optics) in Oto-Rhino-Laryngology

An introduction of the "rod-lens" image relay system with fiberlight transmission opened a new chapter in those oto-rhino-laryngological procedures where rigid endoscopes are employed. These miniature telescopes give a brighter image with a wider viewing field through smaller, more easily introduced instruments. The indirect laryngoscope (90° direction of view) incorporating fiberlight transmission does not exceed 5 mm in total outside diameter. The larynx and the nasopharynx can be examined in one session. It is much more comfortable for the patient because of the small size. The enlarged image can be observed more easily and in greater detail than with the standard mirror technique.

For anterior rhinoscopy a 4 mm telescope with a foroblique view can be introduced with ease through the nostrils. A 2.7 mm rod-lens otoscope with a handle was designed to evaluate its usefulness to replace the cumbersome otoscope with the loop magnifier.

A new set of instruments for bronchoscopy with controlled ventilation and excellent view for the various lobes, including the upper lobe, and an optical biopsy forceps facilitates accurate tissue sampling.

Foreign body removal with these instruments under telescopic control—mainly in pediatrics—opens new vistas for this difficult task.

George Berci, m.d.

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The Use and Management of Cuffed Endotracheal Tubes

The incidence of chronic airway obstruction by subglottic and tracheal stenosis has risen sharply in the last 15 years. This is part of the price paid for the increased popularity of nasotracheal intubation in newborns, and for the use of cuffed endotracheal and tracheotomy tubes in older age groups. A portion of this price must be accepted as a necessary risk outweighed by increased survival rates and the benefits of positive pressure respiratory support. However, stenosis afterwards is the direct result of trauma to the glottis and trachea caused by these tubes, most of which can be avoided by using some common sense.

Two conditions predispose in stenosis, infection and poor mechanical fit. A tracheal infection may be pre-existing or caused by poor sterile technique in subsequent management. The latter is preventable by good care. The former is sometimes preventable by selective use of tracheotomy in patients where inflammation of the larynx or subglottis is the primary airway obstruction or when intubation is anticipated to be needed for more than three days.

A poor mechanical fit of any type of tube causes mucosal and even cartilage destruction by direct pressure or avascular necrosis. In the newborn period, this is almost always caused by inexperienced operators, multiple intubations within a few days, and the temptation to use too large a tube to obtain a "snug" fit. While such a tight fit can be comforting to the physician at the moment, it is almost a guarantee of postintubation edema and respiratory distress 8 to 24 hours afterward, again requiring intubation, and the cycle begins.

In older children and adults the mechanical causes increase in variety. Sustained or overinflation of a cuffed endotracheal or tracheotomy tube is probably the most common preventable cause of stenosis. It is better to use a fairly large tube with a cuff needing only slight expansion than a smaller tube which requires a greater air pressure in the cuff to occlude the tracheal lumen. No cuff should be left expanded for longer than absolutely necessary, and periodic deflation every two or three hours should be a routine nursing order in hospitals where personnel can be trusted not to overinflate the cuff. The use of soft pliable materials for both endotracheal and tracheotomy tubes can prevent further tracheal trauma. When tracheotomy tubes are used, especially in children, a postoperative lateral x-ray of the neck and upper mediastinum is good medical practice to check on the location and fit of the tube to prevent posterior wall necrosis and esophageal problems. Endotracheal bleeding, even if very minor, should always be considered a sign of a poorly fitting tube until proven otherwise.

F. Blair Simmons, m.d.

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Sudden Sensorineural Hearing Loss

In spite of the fact that sudden spontaneous sensorineural hearing loss is a medical emergency, it is probably the most frequently missed diagnosis in otology. In the typical case, an otherwise healthy adult notices a "stuffy" or "full" feeling in one ear. Tinnitus may be present, but vertigo is uncommon. This feeling may disappear spontaneously in a few hours. If it persists, he will probably see a physician within the first two days, but this is likely to be unrewarding since the chances for a correct diagnosis are less than 50 percent, even for an otolaryngologist (unless the hearing loss is nearly total). Instead, the average patient will be treated with decongestants, middle ear inflation, and perhaps antibiotics in the assumption that the cause is eustachian tube obstruction and middle ear air pressure changes.

Fortunately, many patients recover in spite of this treatment. Those who do not are statistically likely to finally have their hearing tested about one week later, after the most favorable therapeutic interval has already passed. Causes for these losses and their treatments vary, but one factor common in all studies is an impressive correlation between time of diagnosis and prognosis. For example, those discovered within two days of onset have a 50-50 chance for complete recovery. If discovery is delayed until six weeks, chances for even a modest recovery are less than 5 percent.

There are over 15 proposed causes for sudden hearing loss reported, some treatable, some not. The most common causes are considered to be viral infections, intracochlear membrane breaks, vascular spasm, several blood disorders, autoimmune disease, meningitis and syphilis. Treatment depends upon most likely cause, but until this is established by laboratory tests, which should include a cerebrospinal fluid examination in most cases, additional trauma to the ear should be avoided by restricting physical activity for the first few days after onset and by not attempting to forcibly inflate the middle ear.

F. BLAIR SIMMONS, M.D.

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Vertigo in "Whiplash Injuries"

So-called "whiplash injuries" cause many symptoms which seem difficult to explain on the basis of the trauma involved. A large number of these unfortunate patients complain of "dizziness" and, before the availability of electronystagmography, were thought to be "crocks" in search of a "cabbage poultice." By using electronystagmography to search for spontaneous and positional nystagmus, however, at least half of these patients complaining of dizziness can be demonstrated to have pathologic change in the balance system. The pathologic lesion may be in the peripheral labyrinth, eighth nerve, cerebellopontine angle, brain stem, cervical musculature, vertebral arteries, or the intervertebral discs, or any combination thereof. Any patient complaining of "dizziness" after a "whiplash" injury should be subjected to a complete evaluation of his balance system.

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Posterior Sinus Approach for Nosebleeds

Nasal bleeding may be so profuse and persistent that it taxes both the patient's and the physician's endurance and may endanger the patient's life. The most severe bleeding usually occurs in the posterior nasal area from branches of the internal maxillary artery. Posterior and anterior nasal packing has been the classic treatment of postnasal bleeding and is successful in at least 80 percent of cases. The maxillary sinus approach for ligation of the internal maxillary artery is usually successful in controlling the packing failures.

The antrum is entered similar to a Caldwell-Luc operation under local or general anesthesia, depending on the condition of the patient. The operating microscope permits excellent visualization for removal of the posterior sinus wall and dissection of the internal maxillary artery in the pterygomaxillary space. The internal maxillary artery and all its branches are ligated with neurosurgical clips. Nasal packing can usually be removed immediately.

The indications for this procedure are as follows: (1) Any patient who has required repeated packing for epistaxis; (2) any patient who rebleeds upon removal of the pack; or (3) where the bleeding is not controlled by a well-inserted anterior and posterior pack. Some otolaryngologists now advocate internal maxillary artery ligation as the initial procedure for posterior epistaxis.

R. MELVIN BUTLER, M.D.

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Cryosurgery in Otolaryngology

Cryosurgery is described as a mode of applying cold as a therapeutic agent. Cold compresses as a mode of therapy were used back as early as 2500 B.C. The use of modern-day cryosurgery was begun in 1961 when Cooper and Lee described the cryogenic system attaining temperatures as low as −190 degrees centigrade. At this time, most of the cryosurgery was done in the neurosurgical field, but with the new versatility of the cryosurgical methods, other fields of surgery have turned to this mode of therapy. The cryobiology of this method is based primarily on the vascular flow within the tissue involved as well as its rate of crystalization. The physical chemical factors underlying the cell injury and freezing have been widely investigated as well as the immunological properties of freezing. Use of cryosurgery is primarily indicated in diseases of deficient blood clotting where open surgical procedures might be a hazard. Investigative work in this field is continually in progress. More recently, it has been found that by decreasing the vascularity within the involved tissue, as with epinephrine compounds, the extent of tissue destruction can be decidedly lessened, thus extending the usefulness of the modality.

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Hearing Aids and the Pre-School Child

The acquisition of oral speech and language by the hearing handicapped youngster is dependent upon his receiving auditory input within the first three years of life.

Techniques for selection of appropriate hearing aids for children have advanced considerably in the past several years. A hearing loss may be diagnosed, the degree of loss estimated and the approximate audiometric slope or curve may be charted for an infant as young as three months of age. An experienced audiologist is able to use specification data and select a trial aid on the basis of frequency and intensity response curves, distortion and output information, durability and compactness. Hearing response to voice, warble tones, and taped sound stimuli may be compared unaided and aided. It is extremely important after the aid is issued that the parents consult periodically with the audiologist. Auditory training procedures are outlined, techniques of language stimulation are suggested, the mechanics and proper care of the instrument is described. This consistent follow-up with the parents, teachers, hearing therapist and child is usually a guarantee that the child will achieve maximum benefits from amplification. It is now agreed throughout the otologic-audiologic profession that this early awareness of sound environment and the integration of auditory with visual communication is essential to the rehabilitation of hearing handicapped children.

SHIRLEY SCHRIER, M.A.

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Rhinoplasty

In the past few years, more emphasis is being placed on conservation techniques in the surgical treatment of nasal deformity. Incisions are now planned to offer maximum exposure of the internal structures of the nose with minimum destruction of the mucous membrane and skin, thus lessening atrophy and the formation of scar tissue.

Better understanding of the physiologic function of the nasal septum with the relationship of the nasal pyramid is being stressed. Not only is cosmetic result important, but the maintenance of a functional airway is emphasized. The anatomic relationship of the upper and lower lateral cartilages with the nasal septum and how they affect breathing are important considerations.

In the ideal result the patient has excellent nasal function as well as a good cosmetic appearance. Therefore, the accomplished rhinologist strives to attain function as well as beauty.

Meyer Schindler, M.D.

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Microscopic Laryngoscopy

In the last three years, fiberoptically illuminated laryngoscopes have been developed which, by their brilliant light and improved design, permit use of the operating microscope during laryngeal surgical procedures. The operating microscope, with stereoscopic magnification, assists in the precise removal of lesions such as singer's nodules, polyps and leukoplakia, from the vocal cords. Magnification of 6 to 10 times favors complete removal while preserving the substance of the vocal cord. Use of the operating microscope also permits early identification and excision of malignant vocal cord lesions while they are still extremely small.

Herbert H. Dedo, M.D.

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Conservation Surgery of the Larynx

Conservation surgery is the term given to the laryngeal procedures which totally remove malignant lesions in selected cases while preserving one or both vocal cords and thus the patient's voice. Two such procedures are vertical hemilaryngectomy and supraglottic laryngectomy. Vertical hemilaryngectomy can be used to remove a localized lesion that is limited to the superficial layers of the true vocal cord, occasionally even after a full course of radiation therapy has failed. Supraglottic laryngectomy can be used to remove cancers limited to the false cord, aryepiglottic fold, epiglottis, base of tongue and piriform sinus. It is usually preceded by a partial dose of radiation therapy when the lesion involves the pharyngeal mucosa. Since so many of the patients with supraglottic malignant disease are in active middle life and anxious to return to work, preservation of the voice is especially desirable.

Herbert H. Dedo, M.D.

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Audiologic Evaluation in Newborns

Identification of hearing impairment as early in life as possible has been recognized and implemented in numerous newborn nurseries in the United States.

Downs and Hemingway (1969) found the incidence of hearing loss at birth to be one in

1,000 in their study of 17,000 newborn infants. Another estimate (Downs and Sterrit, 1964) found that peripheral hearing impairment may appear in one of every 2,000 babies.

The Joint Committee on Newborn Hearing Screening Program, February, 1971, issued the following statement on the subject of newborn testing: "Review of data from limited number of controlled studies which have been reported to date has convinced us that results of mass screening programs are inconsistent and misleading."

However, the final recommendations of the conference do include identification of newborns by prenatal history and postnatal physical assessment of the infant. This would include babies who have a family history of deafness, rubella, congenital malformations of the external ear, cleft lip or palate, infants having a bilirubin value of 20 mg percent or more, who had exchange transfusions at high risk of bilirubin encephalopathy, all infants under 1,500 grams of weight, and all infants with abnormal otoscopic findings.

In view of the controversy of infant testing, there appears to be a general consensus that we do need some kind of auditory screening or an auditory high risk register at the time of birth to detect early deafness.

JANICE R. SIEGEL, M.A.

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Laryngeal Edema and Corticosteroid Therapy

There are three major types of laryngeal edema which need to be differentiated before therapy can be begun. These vary according to the location of the obstructive edema.

Acute epiglottis. This is an acute infectious edema of the epiglottis. When it occurs in children it represents an emergency and usually requires tracheotomy. It is characterized by inspiratory as well as expiratory stridor, difficulty swallowing, drooling, and the appearance of a large, rounded, cherry-red epiglottis visible above the posterior third of the tongue. Since these are usually streptococcal infections, large doses of penicillin administered promptly are most effective. Corticosteroids have no place in the treatment of acute epiglottis. If tracheotomy is not performed, the airway must be watched very closely until the edema subsides.

Acute laryngitis. This is characterized by hoarseness or complete loss of voice. There is no respiratory distress since there is an adequate glottic airway. This type of edema involves the true vocal cords and is usually caused by voice abuse or chemical irritation of the vocal cords. The treatment consists of simple voice rest, absolute abstinence from smoking, and occasional steam inhalations. Corticosteroids are used only in severe cases where rapid resolution is necessary—for example, in the treatment of opera singers.

Acute laryngo-tracheo-bronchitis (croup). This is an inflammatory disease of the lower respiratory tract consisting of severe inflammatory edema of the conus elasticus region just below the true vocal cords. The onset of the condition is characterized by rapidly developing inspiratory stridor, the typical barking sound of a croupy cough, and the presence of a relatively normal voice. It is in this condition that the proper administration of corticosteroids is extremely important and will nearly always obviate tracheotomy.

The treatment of acute laryngo-tracheo-bronchitis consists of the use of a cold mist croup tent (croupette), antibiotics, and steroids. Since the infectious organism is most commonly alpha-hemolytic streptococcus, Hemophilus influenzae, beta-hemolytic streptococcus, and Staphylococcus albus, in that order of incidence, ampicillin is the drug of choice. Corticosteroids should be administered intravenously or intramuscularly in large shock doses. Since adrenal suppression is not a factor to be considered here and since the treatment is aimed at rapid resolution of tissue edema, the initial dose should not be less than 100 mg of soluble hydrocortisone (Solu-Cortef®) or 40 mg of methylprednisolone (Solu-Medrol®), even in small infants. If the initial dose fails to relieve the respiratory stridor, a second dose of equal strength should be given one hour later. A "maintenance dose schedule" is ineffective and should be avoided. Unless a patient is in extreme respiratory distress on admission, requiring immediate tracheostomy, all cases of laryngotracheo-bronchitis can be successfully treated with the early administration of large intramuscular doses of corticosteroids.

JOHN A. T. ROSS, M.D.

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Management and Treatment of the Neck Mass With the Unknown Primary

In adults the presence of a lateral neck mass must be considered evidence of malignant disease until proved otherwise. A thorough search of the head and neck including careful and repeated visualization and palpation of all appropriate cutaneous and mucosal surfaces, direct and indirect laryngoscopy, nasopharyngoscopy, diagnostic radiographic evaluation of the chest, paranasal sinuses and esophagus must be carried out.

Despite these and further diagnostic procedures, in about 6 percent of the patients in whom the neck mass is eventually diagnosed as a metastatic carcinoma, no primary lesion is found. It is at this point, and not before, that needle or open biopsy should be performed. The former will produce minimal dissemination of tumor cells and ensure the least compromise of subsequent therapy. The surgeon and patient must be prepared for definitive operation (radical neck dissection) at the time of an open frozen section biopsy.

Irradiation would be the treatment of choice for undifferentiated carcinoma, lymphoma, or squamous cell carcinoma located in the posterior triangle of the neck (most probably metastatic from the nasopharynx, in which case the nasopharynx would also be irradiated). Otherwise, neck dissection is performed either alone or in continuity with the primary, if identity of its locale can be gleaned from biopsy. If it proves to be a squamous cell carcinoma, blind biopsy of the nasopharynx, the tonsils and the base of the tongue is performed during endoscopic examination under general anesthesia. In a large series reported there was a 30 percent three-year survival, and 25 percent five-year survival with the primary sites eventually identified in 31 percent, the rest remaining occult.

FREDERICK M. TURNBULL, M.D.

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Catecholamines

A Product of Clinical and Basic Science

In this issue of California Medicine we read that the basic scientist and clinician have developed a deep understanding of the pharmacologic features, synthesis and metabolism of catecholamines. As the scientist and clinician have applied their knowledge to medical practice, focus has once again been drawn to what may be called a recurrent cycle of interdependence between them. The value of this cycle is great and is apparently expected and certainly rewarded by the public which supports us. However, the threads which bind together the segments of medical science and practice are vulnerable. Indeed many in the profession wonder if they exist. This editorial proposes to further an awareness of the cycle and indicate its value to both the scientist and clinician. Only as we become aware and appreciative of the cycle will we conscientiously foster its continuance through frequent and intellectually stimulating contacts. These contacts, I believe, advance the standards of medical practice and the maintenance of scientific productivity. An analysis of the history of obtaining and using data related to catecholamines illustrates the cycle well, and fosters an appreciation of it.

If norepinephrine and epinephrine had little effect in man, would we have learned so much about the details of their pharmacologic effects? Without knowledge of the cardiovascular effects of catecholamines, would the pathogenesis of diseases like pheochromocytoma, Riley-Day or Zetterson's syndrome have been linked to abnormalities of catecholamine synthesis or metabolism? If such abnormalities had not attracted clinicians, would we have pressed for, provided, or even considered, funding for the investigations which led to a further realization of the pharmacologic potential of catecholamines?

We have learned that catecholamines affect many systems in addition to the cardiovascular. In part, the symptoms seen in patients with diseases characterized by excess production of or unusual sensitivity to catecholamines have justified and stimulated research on the pharmacologic properties of catecholamines. For instance, once we knew that catecholamines were present in selected areas of the brain, that drugs which altered the content or turnover of catecholamines altered mood, sleep, or behavior, and that patients with pheochromocytoma had mental aberrations and paresthesias, we had justification to question whether systematic administration of catecholamines, their precursors, metabolites or congeners could mimic selected neurologic diseases or possibly cure them.

After neurophysiologists had indicated the function of the basal ganglia and chemists had indicated their unique content of dopamine, and after dopamine concentration was found diminished in the basal ganglia of patients with Parkinson's disease, the stage was set for a series of experiments which revealed one of the most dramatic pharmacologic ameliorations ever known to neurologic disease. Medical investigators reasoned that because primary amines did not freely cross the blood brain barrier, dopamine administration would have little chance of replenishing the dopamine content of the basal ganglia. They chose the amino acid dopa because biochemists had indicated that L-amino acids were actively transported into brain, and L-amino acid decarboxylase was present in the central nervous system where the drug must be converted to dopa-

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mine. Even with this knowledge, the first groups to administer dopa found no effect in patients with Parkinson's disease. Had it not been for well-documented principles of drug administration, formulated by pharmacologists and clinical pharmacologists, perhaps Cotzias would not have been so courageous and persistent in administering large doses of drug for long periods. The successful treatment was further refined after clinicians noted side effects of long-term administration of dopa that may have been due to the peripheral rather than central effects of dopamine. Pharmacologists were able to propose that drugs which block the peripheral but not the central nervous system decarboxylase activity could be useful in (a) limiting conversion of dopa to dopamine in peripheral tissues (therefore limiting the "peripheral" toxicity of any dose of dopa, and (b) allowing lower than ordinary doses to produce a given central effect, since a greater percentage of any given dose would be transported into the brain when the peripheral decarboxylase was inhibited.

The pharmacologists' proposals have been clinically realized. Furthermore, it is quite likely that the principle illustrated by these experiments will be applied to other therapeutic settings. In general, it will not be surprising to find that amino acid drugs which work centrally can be given in lower doses and with fewer side effects when their distribution to the brain is enhanced by a peripheral decarboxylase inhibitor. There is no serendipity here—rather, these are the results of forethought facilitated by communication.

The clinician may also establish where available knowledge is insufficient to explain certain symptoms of a complex attributed to excessive catecholamines. Because we have studied the pharmacologic properties of catecholamines, we know that the diarrhea associated with neuroblastoma or ganglioneuroma, the abnormalities of serum calcium, the appearance of flushing and hypotension, and the variation of symptom complexes in patients with pheochromocytoma cannot be explained by simple increases in catecholamines in the plasma. Thus, the clinician forces the scientist to return to his bench and, by this maneuver, the clinician has opened new areas of endeavor and understanding. His curiosity has propelled the scientist toward the evidence that tumors may be pluripotential, that there is a molecular relationship between catecholamines and insulin release and effect, or between catecholamines and gonadal or renal function. From the data in the symposium on catecholamines, the clinician may encourage the scientist further and may even say, "Thank you for demonstrating that alpha-mimetic amines inhibit insulin release, but help me to explain why, when alpha-adrenergic blocking agents reverse the abnormal insulin response in patients with pheochromocytoma, the glucose tolerance is still abnormal."

As the scientist returns to his bench and tubes, he could and should indicate that he cannot yet answer that question but he can issue some caveats. Since he has elucidated a profound effect of catecholamines on the physiologic response to glucose, vasopressin, and gonadal hormones, he might warn that serious disruption of physiology may occur while a patient is being treated for his obesity with amphetamines or with catecholamines in general. In addition, since beta-mimetic catecholamines may seriously alter the function of human leukocytes (not described in the symposium), the scientist may legitimately ask that the clinician observe carefully the patient receiving catecholamines during the course of an infection or inflammatory disease for evidence of specific effects of the drug that might be attributed to its newly found action on leukocytes. So the cycle continues, with potential benefit to all participants.

We should note the application of knowledge concerning the synthesis and metabolism of catecholamines. Aside from the obvious advantage of having stimulated intellectual efforts which resulted in at least two Nobel prizes in recent years, without this information clinicians might still be treating essential hypertension with rice diets, surgical sympathectomy or, at best, toxic ganglionic blocking drugs or Rauwolfia alkaloids. Instead, drugs that can competitively or noncompetitively antagonize the pharmacologic effects of catecholamines have been developed and have helped both in the diagnosis of diseases of catecholamine excess and assessment of the relative contribution of epinephrine and norepinephrine to a variety of diseases and physiologic states. The same drugs also contribute to the therapy of those diseases they help to discover.

Without a knowledge of metabolism we would have been unable to diagnose unequivocally pheochromocytoma with simple chemical techniques, and would also have been unable to design drugs to interfere selectively with the function of the autonomic neurons and ganglia. Knowing the fine details of synthesis has allowed us to pinpoint rate-limiting steps in the formation of catecholamines and to design competitive inhibitors of critical enzymes (tyrosine hydroxylase and dopamine beta oxidase) that can lead to true decreases in the rate of catecholamine synthesis. These drugs (for example, alpha methyltyrosine) have been extraordinarily useful in selected instances of pathologic overproduction of catecholamines. Very likely, with the help of organic chemists and molecular pharmacologists, we will be able to design safer drugs, with great tissue specificity, that can be used to alter the modulating role of catecholamines on such diverse functions as glucose tolerance, hunger and obesity, sleep and inflammation.

The scientist may offer additional discoveries in the future. What will be the pragmatic importance of understanding more of the chemistry of the granules of the postganglionic nerve ending? Will there be clinical uses of medical sympathectomy, for example, with 6-hydroxy dopamine (not covered in the symposium)? If the past is any indication of the future, the clinicians will put such information to good use. Maybe they will also ask the scientist if stimulation of the gut by catecholamines will raise its cyclic adenosine 3′, 5′-monophosphate (AMP) content, as does cholera enterotoxin that causes the severest of diarrheas.

The example of applying basic facts concerning catecholamines to medical settings is not at all unique, nor are the vignettes of mutual dependence described in this editorial or in the symposium at all inclusive. An intimate interdependence between scientist and clinician utilizes fully Koch's principles that apply philosophical logic to science.

Objectivity about gains in medicine and science indicates what the public should have reinforced: that no single group deserves overwhelming accolades for the health benefits the people receive. Rather, it is the joint effort which merits praise. If success (to scientist, physician, patient and patron) is to be continued and consistent, the bonds of this interdependence must be defined and applied, and the results of this union must be demonstrable.

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Health Science and "Humanization"

THE SPECIAL ARTICLE by Professor Clark Kerr, formerly president of the University of California and now chairman of the Carnegie Committee on Higher Education, which appears elsewhere in this issue calls attention to what may be a most important role of medical and health science in the future of higher education in this nation. Dr. Kerr suggests that social changes which have already begun will profoundly influence higher education for many years to come. He notes that there is likely to be greater social emphasis on "humanization" with greater interest in a better access to a high quality of life for more people and with more attention being paid to the individual needs of people. In this connection he predicts "golden decades" ahead for the health sciences in terms of opportunities to do more and more for the American people. He stresses that the "health sciences are not only more central to the welfare of our people as a whole, but also more central to the conduct of higher education as our best contact with the people, our best service to the people." He goes further and says, "It may come to be that the greatest help that higher education will receive in this 'time of troubles' will be from the success of the health professions."

These are words to ponder for physicians and medical associations, as well as for medical educators. They suggest that the health professions will in the future, as is even now the case, be concerned with more than the prevention and cure of disease, although this will always remain a primary responsibility. In addition to this he is of the opinion that the health professions are destined to become inextricably involved in what may be called the "humanization" of human society and with it higher education. A concern with human individuality and the quality of human life is actually nothing new for physicians, who have always been more concerned with more aspects of human individuality than any other profession. And they have traditionally striven to help their patients reach and enjoy the highest quality of life that their personal situation would allow. So perhaps what may need to be done now is to extend the reach of medicine and health science so that what has been traditionally done for the patient can begin to be done for society as a whole.

It happens that there is a special opportunity in California to do something tangible right now to strengthen the base of medical and health science in our institutions of higher education. Five of California's eight medical schools are in the University of California system. On the coming November ballot there will be a proposition for a bond issue to provide funds for essential construction and essential improvements in the facilities of these schools of medicine and health science. The CMA Council strongly supports this bond issue and urges the physicians of California to do everything they can to get it passed. By doing this they can take an essential step to create a firmer base of medical and health science in higher education in this state, a step absolutely necessary for the production of health personnel who are needed now, and in preparation for whatever "golden decades" there may be ahead for the health sciences. It will be tragic if this great state is not prepared both to fulfill its immediate needs and to realize its longer range opportunities.

Drug Interactions

Drug interactions are the pharmacologic sequelae attending the simultaneous use of two or more drugs, which may result in enhanced or diminished drug effect. Drug interactions may be direct, dependent on the chemical or physical properties of the drugs involved, or indirect, the reaction to a second drug being mediated by pharmacologic changes in the patients elicited by the first drug given.

The frequency of drug interactions in clinical practice is only now becoming apparent. In the past few years, a host of publications dealing with this topic have appeared in the clinical literature, more than a hundred commonly used drugs being involved. Additionally, epidemiologic studies have shown that the incidence of adverse reactions when patients take fewer than five drugs is approximately five percent. When patients are given 20 or more drugs, the incidence of adverse reaction rises to 45 percent. The expotential rise of adverse reactions during multiple drug therapy strongly suggests the possibility of drug interactions.

Elsewhere in this issue of CALIFORNIA MEDICINE, Jack N. Turner has assembled "Some Potential Interactions Between Prescribed Drugs and Over-the-Counter Products." We are a drug-taking society at least in part because of the success of the advertising agencies' ability to convince us to take medication for trivial or self-limited conditions. Commercial blandishments and the ready availability of non-prescription drugs in food stores and even saloons mislead patients into believing that these substances are harmless. The study by Ronald B. Stewart and Leighton E. Cluff cited below disclosed that 98.3 percent of patients who had taken prescription medications in the month preceding a clinic visit had also administered non-prescription medications to themselves during that same period. Turner asserts that practically all over-the-counter drugs should be available only on prescription. This position has its merits but is not currently practical, as we would not have enough physicians to write the prescriptions and it seems unlikely that the public would accept legislation that would drastically reduce their access to non-prescription drugs. As physicians become more familiar with the problem of drug interactions, they will likely devote more time to patient education about the hazards of multiple drug therapy, including exposure to non-prescription items.

The article by Turner brings into focus another problem involving drug interactions. It is very difficult to keep them all in mind. The number of drugs involved in interactions and their complex interplay with disease states will eventually require computer methods to store information about known interactions and to prospectively predict potential drug reactions based on information regarding chemical and pharmacologic properties of the agencies given for diseases. Such a warning system would not limit a physician's prescribing prerogatives, as not all potential drug interactions occur in all patients and the physician's therapeutic goals may be worth some risk. Nor would a computer system reduce the physician's obligation to monitor patients receiving multiple drug therapy with great care to detect previously unrecognized drug interactions and thus to expand the computer's "knowledge." For the time being, physicians and their patients must be convinced that multiple drug therapy is considerably more dangerous than single drug therapy, which itself is hazardous enough.

HOWARD F. MORRELLI, M.D.
Vice Chairman for Housestaff Affairs
Department of Medicine
University of California, San Francisco

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A Proposition for the Health Sciences

AS PHYSICIANS TO THE PEOPLE of the state of California, we must accept our share of the responsibility to insure that on November 7 California's voters endorse Proposition Two, the measure that would implement the Health Science Facilities Construction Act.

It is imperative that physicians in this state, between now and November, inform as many citizens as possible, by informal conversation with patients and acquaintances and speaking engagements before service clubs and other local organizations, about the need for passage of this proposition.

Proposition Two is vital to continued and improved health services for Californians. It is a $155.9-million bond issue that would enable the University of California to complete construction of medical schools at Davis, Irvine and San Diego and to bring up to standard a number of educational buildings for medical, dental, nursing, optometry, pharmacy, public health and veterinary medicine students in the University system. Indeed, the future of the three newest medical schools may be in jeopardy if Proposition Two fails.

By actions of its Council, our California Medical Association has taken several important steps in support of Proposition Two. It has voted to:

- Endorse Proposition Two, which is consonant with previously stated policy.
- Reaffirm the need for the educational facilities that Proposition Two would provide.
- Contribute $5,000 plus staff services to help pass Proposition Two.
- Call upon all physicians to speak out in favor of Proposition Two and individually to contribute funds to help inform all Californians of the need for its passage.

JEAN F. CRUM, M.D.
President, California Medical Association

COLECTOMY FOR ULCERATIVE COLITIS

Colectomy is the surgical treatment of choice in ulcerative colitis. We don't wait as long as we used to before recommending this procedure. If the patient has severe ulcerative colitis which is interfering with his life, if he has lost more than a quarter of a year from work, this is the time to start talking about colectomy. Ten years ago we used to consider it a personal defeat if the surgeons got hold of any of these people. But I have become convinced, after seeing people with ileostomies go back to work and resume their normal lives, that a mutilating procedure like a total colectomy may be better than being chronically ill. If the individual is refractory to medical therapy, if he continues to lose ground despite medical therapy, if he is unable to continue with his work, if his x-rays show advanced disease, usually in these cases I would at least start talking to the patient about colectomy.

—RAMON R. JOSEPH, M.D., Ann Arbor
Extracted from *Audio-Digest General Practice*, Vol. 19, No. 22, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

LETTERS *to the Editor*

A Call for Help

To the Editor: In my capacity as psychiatric consultant to public health nurses in one of the Bay-area counties, I have become more and more troubled by the following observation. I see a great number of patients who in addition to, or often as a direct consequence of, their physiological illness are struggling with painful, often disabling, sometimes lethal emotional problems (for example, suicidal depression). I am troubled by seeing that prior to the public health nurse's request for a psychiatric consultation, nobody seems to have called in a psychiatrist, even though the patients had been in treatment already for quite a while by a number of physicians, and sometimes even told their doctors openly how they felt. The physicians responded by prescribing psychotropic medications, giving reassurance and using "good bedside manners," making referrals to nurses, welfare and social workers; but seemed reluctant to call upon a fellow specialist, the psychiatrist. (Yet I feel it safe to assume that the very same physicians would not have hesitated to call in a surgical or internal specialist rather than referring the patient solely to a podiatrist or dietitian, useful as the latter may be in certain circumscribed situations!)

Why is this? Why this apparent reluctance on the part of physicians for a psychiatric consultation for anything but the most blatantly psychotic patient? — Or is my experience entirely atypical? — Whatever the reason, whatever the case: I would like to know; I think we all should like to know!

Could we have become so preoccupied with multiphasic blood chemistries that we miss the emotional "cry for help" of the patient? Or do we secretly believe that emotional problems are "all in the mind" (= imaginary) and can be treated with "plain common sense" instead of specialized expertise? — Or have our non-psychiatric colleagues become disillusioned by us psychiatrists because we may have hidden behind the screen of the "sacred therapeutic hour" instead of responding to emergencies? Or have we distressed them with our non-directive psychiatric jargon when they wanted practical advice in plain English?

My purpose is not to find a culprit: my purpose is to understand the problem (if it is really as prevalent as it appears to me), and to find solutions. Maybe someone will ask for a NIH grant to research the question: I have no such ambitions (and the results may be outdated by the time they are published). The CMA may see fit to query our membership on this: but that too is not for me to decide.

What I do ask is this: when this letter is published, would all those who read it, psychiatrists and non-psychiatrists alike, be kind enough to let me have their opinion based, if possible, on their experiences with medical-psychiatric consultations? Maybe this could be done with sufficient discretion and anonymity to avoid even embarrassing anyone.

The question is: "Why this apparent reluctance to ask for psychiatric consultations?" — Please do help me to find the answer.

EDMUND F. KAL, M.D.
440 Davis Court
San Francisco, Ca. 94111

The Pajaroello in Petroglyphs

To the Editor: As an epilogue to "The Pajaroello Tick Bite" (California Medicine, May 1972) the authors wish to share with your readers the following bit of historical data.

Scattered through the San Rafael wilderness of the Los Padres National Forest (Santa Barbara County) are Indian paintings and carvings, some of which are as much as a thousand years old. In the midwestern portion of the wilderness area at the foot of Hurricane Deck is a large monolith called Pool Rock which is reached by a four or five mile hike into Lost Canyon, which lies between the Manzana and Sisquoc rivers. On the north side of Pool Rock is a cave containing some very well preserved Indian petroglyphs. Grouped on one wall of the cave are found what the Indians of the area considered the "feared and poisonous" animals of the area (see picture). At the top of Figure 1 you will see an oval, bug-like painting (a pajaroello). Beneath this is a headless striped band, undoubtedly representing a rattlesnake; in the right middle area a long-legged structure which most likely represents a lizard or scorpion; and at the bottom a second snake with its head. In the lower frame of Figure 1 is a blown-up print of the pajaroello.

Campbell Grant, one of the foremost authorities on Indian paintings, has included drawings of these particular paintings in his book "The Rock Paintings of the Chumash" (University of California Press, 1965, Plate 15). Mr. Grant concurs with the authors that this painting undoubtedly represents a pajaroello. He noted that it was somewhat unique that "feared creatures" were grouped together and he commented that Indian custom in reproducing such animals invariably depicted them without their head, probably indicating some sort of ceremonial tradition of decapitating poisonous and feared animals.

In conclusion, it is interesting that today we find evidence of ancient fear and Indian folk lore reproduced by the native inhabitants of the area where this tick abounds.

R. M. Failing, M.D.
Santa Barbara

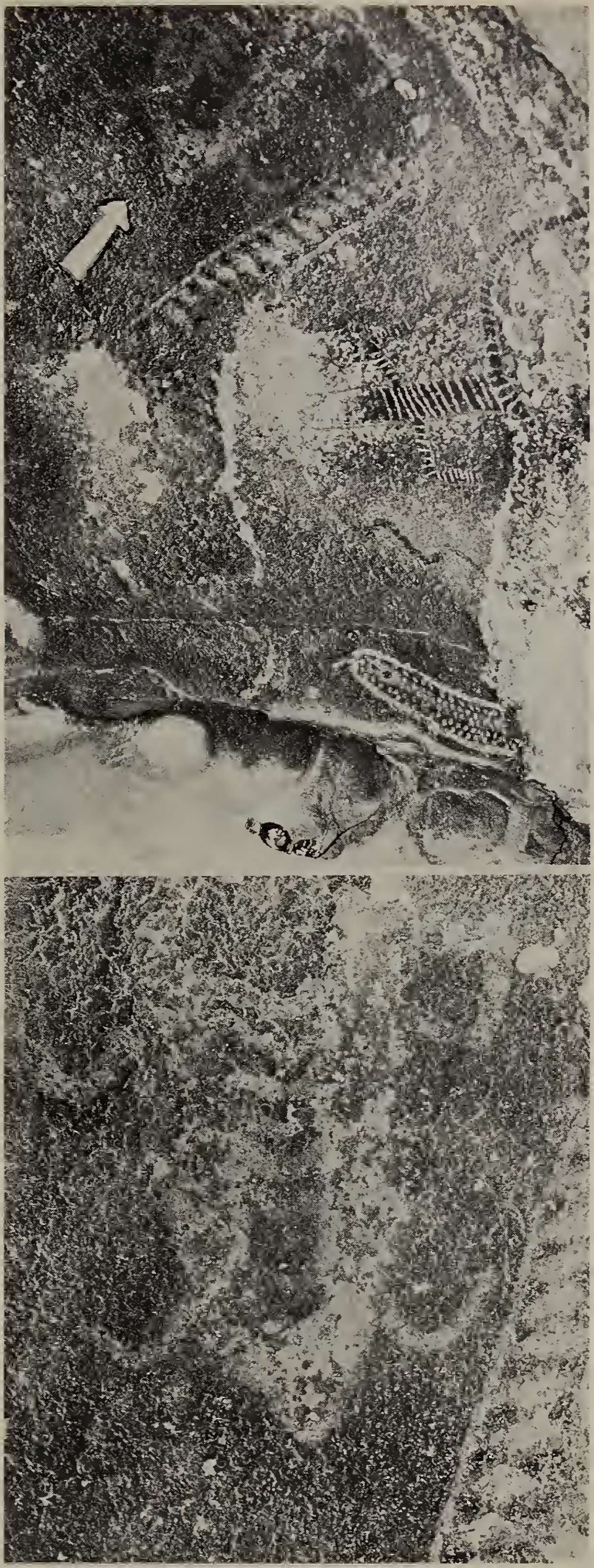


Figure 1.—In upper frame, arrow points to petroglyph of pajaroello, and below it drawings apparently of a rattlesnake and a scorpion. Lower frame is a bigger print of the pajaroello.

Another View of No-Fault Insurance

To the Editor: The recent article by Dr. Rubsamen on no-fault medical malpractice in the July, 1972 issue is too provocative to pass without comment.

Dr. Rubsamen has written a scholarly article with great detachment on this matter. His article suffers, however, in that it leans heavily on precedent and is detached from the realities of the contemporary United States.

The current malpractice problem stems from a conflicting view of justifiable compensation. The law views justifiable compensation only as related to liability whereas the public views justifiable compensation as relating to any injury regardless of cause. In this conflict between the legal view and the public view, medicine loses to the public inasmuch as it is the public which sits on juries. Accordingly, medicine should seek to bring the legal view into line with the public view.

It is time to recognize that we should compensate injury regardless of cause. We must bypass the liability concept. Employers learned this long ago when they set up Workmen's Compensation Boards; there is no reason why the medical profession cannot do the same. None of the objections raised by Dr. Rubsamen are material enough that they cannot be overcome by compensation boards.

The present is propitious for medicine to act on this matter inasmuch as both the university hospitals and the federal hospitals are also being sued for medical malpractice. We have a unique moment in time where the private sector, the university sector, and the federal sector are facing a common problem which is of equal importance to all. Furthermore, a solution is available which is equally advantageous, namely, no-fault medical insurance through compensation boards.

As a practicing physician, I have too much at stake in this matter to accept the advice of an expert who is not actively engaged in practice and who, accordingly, does not fully understand the pressure which current malpractice laws place on the physician in practice. I feel the California Medical Association ought to seek guidance from its members on this matter rather than to rely on an outside expert. I strongly urge the CMA not to accept Dr. Rubsamen's advice and to proceed along the lines suggested above.

What can the membership do to get the CMA to move on this matter?

ARNOLD L. FLICK, M.D.
San Diego

Health Education

To the Editor: The recent report on "Medicine 1980 to 2000" [April, 1972, pages 71-95] confirms that physicians now as in the past, are constantly trying to serve the public; are constantly upgrading their performance in spite of being maligned more or less regularly by the news media. The delivery of health services depends also on a health knowledgeable populace. As long ago as 1940, Dr. E. C. Carlson, in his address to the graduating class of the University of Minnesota, made this statement: "In addition to the 3 Rs, must be added an H, not for hallelujah, but for health." A young mother stated the other day that she had graduated from the grades, high school and college without receiving any education regarding health; she approached her first child totally ignorant and she resented it. Even "Home Economics" in college had been so belittled that most sudents refused to take it.

The information media, on the other hand, both in commercials and in talk programs promote over-the-counter drugs and food faddism, and play up sex and violence. Health education, according to such reporting, consists of teaching youngsters about VD, the Pill, abortion and homosexuality.

If we are going to have an informed public on health matters, that H must be added to the curriculum and the obvious place to start is to make health education a required course for *all teachers*, not only for physical education majors. The curriculum should include physical, mental, emotional and social health. It should be based on anatomy, physiology, human development, nutrition, safety, cleanliness, protection against disease, dental care, vision and hearing protection, human relations, family unity, the optimum age of pregnancy and child responsibility, the hazard of drugs, abortion and of prolonged use of the Pill, and many other factors.

The curriculum should be formulated jointly by physicians, educators, psychologists and sociologists.

H. E. THELANDER, M.D.
Tiburon

Microwave and Man

To the Editor: In reference to the article: Merckel C: Microwave and Man—The Direct and Indirect Hazards and Precautions. California Medicine 117:20-24, July 1972; on page 23, I am mentioned [Column 1, paragraph 2, lines 1-4].

I would call your attention to the fact that the fatality I reported was not due to a ruptured appendix and this was not proved at autopsy.

The paucity of non-lethal effects as mentioned by the author is at variance with the effects on chromosomes described by Heller,[1] and Yao and Jiles.[2]

Our knowledge of the biological effects of non-ionizing radiant energy is limited and the "State of the Art" is not enhanced by published error of omission or commission.

JOHN T. MCLAUGHLIN, M.D.
Glendale

[1] Heller JH: Cellular Effects of Microwave Radiation—Biological Effects and Health Implications of Microwave Radiation, Symposium Proceedings, 116-121, 9/17/69. USD HEW

[2] Yao KTS, Jiles MM: Effect of 2450 MHZ Microwave Radiation on Cultivated Rat Kangaroo Cells. IBID 123-133.

EDITOR'S NOTE: The cited case was reported by Dr. McLaughlin in *California Medicine* 86:336-339, July 1957. The appendix was described in the pathologist's report as intact with proximal stenosis, and the lumen contained and the surface was covered with sterile pus. There was a subsequent evisceration of the wound and a perforation of the jejunum was found at a second operation following which the patient died. The diagnosis at autopsy was enteritis, type undetermined, with subacute suppurative peritonitis.

IF YOU THINK IT'S SHOCK, CATHETERIZE THE BLADDER

The first thing you do when you suspect shock is put a catheter into the patient's bladder and say to yourself dogmatically, "If this patient can put out 20 to 30 cc of urine per hour, he is not in shock." I will tell you, if I must use a statistic, that 99.9 percent of the time this is the finest index of perfusion you can have. I am not talking about the patient with diabetes insipidus. I am talking about the average patient in shock. . . .

Now the more sophisticated individual will say, "What about central venous pressure?" I don't like to poke needles into the subclavian veins. I don't like to put a catheter up the basilic and up the cephalic and into the vena cava but if I have to I will. Rarely will I do that if my patient is putting out 20 to 30 cc of urine per hour. But if I can't get the information I need, if I can't get the catheter in, if there is renal damage, then I will have to consider measuring central venous pressure. Measured in centimeters of water, 0 to 5 means hypovolemia; the patient is probably going to need fluids. Six to 12 could mean hypovolemia; check the patient's urine and his clinical signs, but look out. If the central venous pressure is over 15, don't pour a lot of fluids into the patient or you will kill him, because he is hypervolemic.

—PHILIP THOREK, M.D., Chicago
Extracted from *Audio-Digest General Practice,* Vol. 19, No. 27, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Refer to: Johnstone MW: A leg-easing operating stool (Clinical Note). Calif Med 117:86, Sep 1972

Clinical Note

A Leg-Easing Operating Stool

MARSHALL W. JOHNSTONE, M.D., *Pasadena*

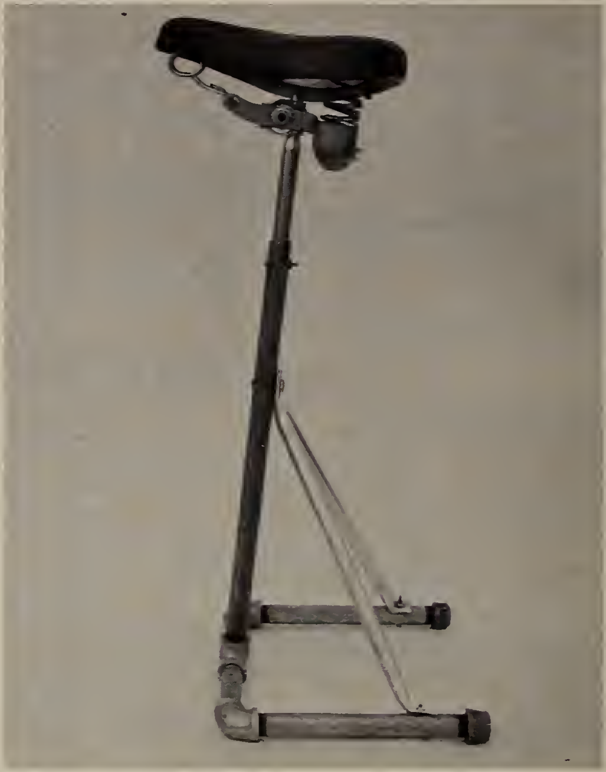
THE OPERATING STOOL PICTURED here is comfortable, effective and inexpensive. Materials for it came from the local bicycle and plumbing shops. Its usefulness is in taking the weight off a sore hip, knee, foot or tired legs. One can sit very close to an operating table and lose only an inch or so of height because the knees are practically straight. Leaning or rocking forward and standing up are easy and safe. The feet are always on the floor.

To make one, you'll need:

One bicycle seat, selected (and padded extra) for comfort
One bicycle seat post (Check to make certain it fits inside ¾-inch pipe as pipe inside calibre varies slightly.)
One 22-inch piece of ¾-inch pipe, threaded on one end
Two 5½ or 6-inch ¾-inch pipe nipples
Two 10-inch ¾-inch pipe nipples
One ¾-inch pipe "T"
Two ¾-inch pipe caps
Two ¾-inch elbows
Two 18 to 22-inch pieces of ½ inch aluminum or electrical conduit tubing, ends flattened in a vice
Four ¼-inch bolts, 1½ inches long, and nuts

Assembly—as in the illustration:

The base is formed first with the two shorter nipples screwed into either end of the "T." Then an "L," long nipple and cap on each side complete the three sided base. The long vertical pipe screws into the "T," and to prevent motion in the threaded joints of the "T," it is braced by tubing. A flattened end of each piece of tubing is bent a little, drilled, and both fastened by a single bolt through a hole drilled at a convenient height on the upright. The other ends are bent, drilled, and bolted to the side base pieces at the points at which they seem to want to rest when the upright is just slightly back of vertical. The seat post slides inside the ¾-inch pipe upright. The height is then tested, adjusted, and fixed by drilling and bolting through pipe and seat post.



I have made three of these seats—first one for the operating room, then one each for my office surgery and my hobby-shop at home. Readers may think of other uses.

Reprint requests to: M. W. Johnstone, M.D., 65 North Madison Avenue, Pasadena, Ca. 91101.

Refer to: Kerr C: The new role of medical education within higher education in the United States. Calif Med 117:87-91, Sep 1972

Special Article

The New Role of Medical Education Within Higher Education in the United States

CLARK KERR, PH.D., *Berkeley*

IT IS A PLEASURE TO PARTICIPATE in this meeting of the California Academy of Medicine and a particular pleasure to respond to an invitation extended to me through my very good friend, Dr. Morton Meyer. Also, it is always a happy occasion when so many people get together who have connections with the University of California and with Stanford. I have had a chance to see higher education around the United States and, to some extent, around the world, and there are very few places where there is such an excellent relationship between two leading universities in the same community. It is rather remarkable not only that there is this good relationship but that here in the Bay Area we should have two of the half-dozen leading universities in the United States. And I know of no area in the world where such a great city and two such great universities have had such supportive relationships among themselves.

My comments are under the title of "The New Role of Medical Education within Higher Education in the United States." I would like to speak first of all about the current state of higher education and then turn to medical education within it. Higher education in the United States has just ended its "Golden Century." This century lasted from about 1870 to about 1970. During that period of time, higher education grew phenomenally. Back in 1870 there were fewer students in all the institutions of higher education than there are now in the University of California alone. Currently, we have about eight million students in higher education and by the end of this decade it will be eleven or twelve million. In 1870, 2 percent of the young people went to college; it is now 50 percent and our Commission is estimating that by the end of the century it will be 66-2/3 percent—two out of every three young people going to some form of post-secondary education. Beyond this fantastic growth in numbers, which can never be repeated again, has been a very great growth in performance. In 1870 the standard institution was a classical college—a four-year college giving the same curriculum to all of its students. Now, in the early 1970s, we have the great modern university, drawing students from homes across the nation and carrying on endeavors which affect almost every person in the United States.

The first great force at work over the last century in creating our modern system of higher education was a great surge of populism, insisting on service to more and more people in more and more ways. The second great force was the introduction of science. The first professor in science was at Yale in 1800, but it was not until about 1870 that science began to expand. Along

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The author is Chairman of the Carnegie Commission on Higher Education.

Presented before the California Academy of Medicine, San Francisco, March 25, 1972.

Reprint requests to: Clark Kerr, Ph.D., Carnegie Commission on Higher Education, 1947 Center St., Berkeley, Ca. 94704.

with science, of course, came research on a larger and larger scale, and graduate training. And out of research came service activities to industry and to agriculture and to the government.

Deep Trouble for Higher Education

One of the great success stories of all human effort on this planet has been the rise of higher education in the United States in the last century. But it is now in deep trouble—probably the deepest trouble higher education has been in since it began, with the founding of Harvard, in 1636. This trouble will not be fatal but for many institutions it is quite severe. The trouble comes from a number of different sources. I will only mention a few.

First of all, there was the student unrest of the 1960's. While we are temporarily going through a period of cessation of that unrest, I think it would be quite unwise for anyone to think that we will never again see student unrest in this country, that we are back to the period of the 1950's and that period will go on forever. As I go around the country and visit a good many campuses, my impression is that, while the students at the moment are not engaged in dissent and disruption as they were a few years back, they are no more satisfied with the state of the United States or the state of the world than they were a few years ago. It is hard to explain why all of a sudden there is this period of inactivity after the period of greatest activism by students in American history; but we do have this period of inactivity at the moment. I think it would be a very foolish person, however, who would say that never again will the students become active on our campuses. The student activism that upset our campuses, also upset the American public in a rather dramatic way.

Beyond the student unrest of recent years, we may be entering into a really new period of human life—something like the change in mentality that took place when the Renaissance came to Europe; or the change in mentality that accompanied the American and the French revolutions, bringing the idea of democracy for the common man. In all of the industrialized nations, we are now going through a "cultural revolution." It is hard to say yet how long it will last and how deeply it will affect our society. In all industrial societies, there is a new emphasis upon the sensate—upon immediate gratification. A long time ago I read an essay by John Maynard Keynes which impressed me very much. It was an essay called "Prospects for Our Grandchildren." And the length of time which has passed since Keynes wrote this essay means that the grandchildren that he was talking about are now here. He said that, as society became more affluent, there would be less emphasis upon saving for the future and preparing for the future; there would be more emphasis upon getting what you could at that moment of time; there would be a diminution in the emphasis on the work ethic which has been so related to the rise of the industrial system. And, in a phrase which I have never forgotten, he said that ever since the industrial revolution began, ever since the work ethic became so important to us, it has always been "jam tomorrow and never jam today"; but that at some point in the future people were going to start asking for "jam today." We may now have reached that period of time.

The Effect of Politics on Universities

The second aspect of the "cultural revolution" is a new emphasis upon the political, a new emphasis upon ideology, a new emphasis upon judging programs and judging people by their political attitudes and affiliations. These two aspects of the "cultural revolution"—and I think they are somewhat in conflict with each other—will have very serious implications for higher education. Higher education is based upon the work ethic. Students study for years and years, and only later get their rewards. But when students want instant gratification and equality of results, it is quite different from the older idea of equality of opportunity rather than equality of results. And, also, when you bring politics into a university, it makes it a much different place; and, from an intellectual point of view, I think a much less satisfactory place. Higher education fought for centuries against the control of the state and the control of the church to develop its own autonomy, and to set up standards of objectivity in an effort at the constant discovery of new truth. But when politics comes into higher education and when ideology becomes a test, rather than the search for the truth, it disturbs higher education enormously. We see some of the consequences of this new "cultural revolution" on many campuses around the country already.

We are in trouble also because we are ending our period of great growth. Since 1870, we have doubled the number of students in higher education every ten to fifteen years, and in the 1960's we went from three million students (on a full-time-equivalent basis) to six million in one decade. This duplicated all the growth between 1636 and 1960. We have some growth ahead in the 1970's, about a 50 percent increase rather than a 100 percent increase. Then in the 1980's, for the first time since Harvard was founded, there will be no increase whatsoever in the number of students for an entire decade. In fact, in some years in the 1980's, for demographic reasons, the number of students will go down. And then again in the 1990's there will be an increase as the grandchildren of the GI's come along. But, beyond the year 2000, higher education will be growing with American society rather than ahead of it. The slowing of growth will make it harder to adapt to new ideas and to bring in so many young faculty.

Serious Financial Problem

Additionally, there is a serious financial problem. In 1960, higher education spent 1 percent of the gross national product. In the intervening period it has gone up to 2.5 percent of the GNP —a fantastic increase; and by the end of the decade it will be pushing toward 3 percent. And the higher that percentage goes, the more resistance there is on the part of the American people to meeting that bill. Also, new priorities are before the American people: to renovate our cities, to conserve our physical environment and to do many, many other things. Likewise, it is going to become more and more evident to the American people that higher education does not increase its productivity as do many other segments of American society. And since we do not increase our productivity, our prices rise faster than prices in general. Our Carnegie Commission has had a study made by the Brookings Institution which shows that the cost per student per year has risen at the rate of general inflation plus 2.5 percent per year. This rising cost per student has been partially hidden by the rapid growth in the numbers of students. We have asked for more money each year on the grounds that we had more students, but in the 1980's we are going to be faced with a different situation. We will have no more students, yet our costs will rise with inflation plus 2.5 percent per year. If you accumulate this 2.5 percent a year for a decade, you get almost a one-third increase in cost. By 1980 we will be spending about $40 billion (in 1970 dollars) a year on higher education, and because of this productivity factor we will have to be asking for about another $12 billion (in 1970 dollars) from American society in 1990—with no increase in the number of students. This productivity factor is going to be catching up with us, so that I do not think that the financial problem of today is a short-term one. I think higher education faces a financial problem for at least the next two decades.

I would like to mention one other factor affecting higher education and causing this "time of troubles." There is a change in the labor market situation. Historically, except for deep depressions, college graduates could always find suitable jobs—jobs that fitted their training. We are now in a transition period in which we have a surplus in some places and a deficit in others. But, before this decade is out, we are going to face a general surplus. The United States Department of Labor estimates that in 1980 only 20 percent of the jobs in the nation will require more than a high school education. And yet we already have 50 percent of our young people going beyond high school into college, and prospectively more than that. Now there is a difference between the flow and the stock you have on hand. The flow changes the stock only slowly but quite obviously, in the long run if you are going to have two out of three young people going to college and only one job in five requiring any kind of college training, you are facing a surplus.

A Surplus of Educated People

And this is going to mean important things for higher education. The public is going to ask why we should spend so much money on higher education when we have more graduates than we can absorb already. A lot of graduates are not going to get the jobs that they expected and we will face somewhat the same situation that has occurred in some other countries around the world—a surplus of educated people. Another impact: historically, wage and salary differentials have been narrowing, so that the people doing the dirty common labor get income more nearly comparable to what trained people in the offices do. As we get this surplus of college graduates, those differentials are going to narrow very, very quickly. Already you can make more money as a garbage collector in the city of San Francisco than you can as an assistant professor in the medical school on the San Francisco campus. And that is going to be happening more and more as you train people out of being common laborers and train them into office occupations. Another implication: historically, we tried to fit the education to the job. In the future, we may be fitting the jobs to the education of the labor force. For example, when a secretary has more education, she is often given more responsibility. This is going to happen throughout American society, and employers are going to have to be prepared to make jobs more interesting, to develop more rotation among assignments, and to assign more responsibility.

These are some of the forces at work which are creating this "time of troubles" for higher education after a "golden century." But within higher education we have four areas which are still quite prosperous, are still growing, still have a great future before them. One of these areas is that segment comprised by the community colleges. The community colleges are politically increasingly popular in state after state. They are generally well respected in their communities.

The second great expansion is going to be in the area of external degrees, of off-campus degrees as are now being given in England through its Open University. I expect a vast increase in the amount of adult education going on across the country, until we really do approach a "learning society" where most of the people, most of the time, are engaged in some sort of learning process.

Another area with a great future is the area of the new electronic technology. We are now facing the fourth great revolution in technology affecting education. The first was when the role of teacher was created and some of instruction was moved from the family into a classroom, however informal. And then the second revolution was when writing evolved; instead of just having oral instruction, you also had written instruction. The third came five centuries ago with the printing press. And now the fourth revolution is coming with the new electronics. As cable TV, computer-assisted instruction, and particularly the video-cassette become more generally available, it becomes possible to turn every living room in the nation into a classroom for higher education.

Education for the Health Professions

And the fourth area is the health professions. As our Carnegie Commission was surveying all of higher education and preparing to make recommendations on its future, we singled out the health professions as an area for particular study because we thought that the health professions were the ones that perhaps had the greatest contributions to make to society and perhaps also to higher education. The health professions within higher education are in a period of comparative prosperity, even as much of the rest of higher education is in its worst depression, and for several good reasons. There is a great demand for more trained people in the health area. The estimates of the Department of Labor are that, if past trends were to continue (and they will not, since adjustments will take place), by the end of the decade of the 1970's we would have a deficit of one million people in the health care fields. Our Carnegie Commission has recommended—and this has been accepted now as national policy—that there should be an expansion of 50 percent in the output of medical doctors in this decade, 20 percent of dentists, and substantial increases of other health care personnel.

Student interests reflect changing situations very quickly. We had a study made last fall of what was happening to applications and to enrollments. Student enrollments in engineering went down 15 percent in one year from 1970 to 1971. In education, they went down 15 percent. In forestry, tied to ecology, they went up 40 percent from the fall of 1970 to the fall of 1971. Nursing had an increase of 19 percent from one year to the next. The biological sciences had a 17 percent increase from one year to the next. In terms of applications, not enrollments, the most phenomenal increase was for law schools where applications rose a little over 50 percent from one year to the next. Medical school applications went up 35 percent from one year to the next. Students are reflecting new possibilities for employment opportunities and for service opportunities in several areas, including the health professions.

A second reason why medical education is going to be more important within higher education is this: higher education once relied upon its schools of agriculture as the best way it had to persuade the public it was useful, and now, in an urbanized society, the health service schools will take their places. Through the health professions, higher education can make a contribution to everyone—an appreciated contribution to everyone, as the schools of agriculture once did.

And, finally, the health professions are becoming increasingly important as intellectual centers within higher education. There are today no other centers in higher education which draw together so many strands of intellectual activity as do the health professions. Increasingly the health professions are becoming the greatest single focal point of scientific endeavor.

So, in conclusion, may I say this: In the last century in the United States we were involved in modernizing our society in the sense of industrializing it and expanding our democracy. And, during this period of time, we added immensely to the capital investment of the nation. We also drew in more and more labor into our cities and industries from Europe and elsewhere around the world, from our farms, and women from our homes. It was a period of great industrialization, great urbanization, great modernization; and higher education exploded along with these trends. And what may be the theme of the next century for American society and for higher education? I would like to suggest that the theme, rather than being modernization, may be "humanization"—more people given greater access to a high-quality life, more attention being paid to the individual needs of people. Whether or not this will be a major theme for American society, it is already a major theme for higher education: to bring in more young people and to give them greater access to the opportunities made available through higher education, and also to pay more attention to the individual needs of students.

In the next century, rather than putting as much concentration as we did in the last century on capital accumulation or the same emphasis upon recruiting labor for the modernized sector of our economy, the emphasis is going to be comparatively more upon increasing individual human capability. The fastest growing part of our society currently is that segment concerned with increasing human capability. We are now spending 8 percent of our GNP on formal education; we are spending 7 percent of our GNP on health, and 3 percent of our GNP on research and development, totaling 18 percent. As short a time ago as 1955, we were spending 11 percent in these three areas. In about 15 years, we have increased the proportion of our national effort devoted to these three areas by more than 50 percent and the percentage is still rising. At the present time—to show how important these activities have become—only 3 percent of our GNP is represented by primary agricultural production. Education and health, each by itself, now constitutes twice as great a proportion of the GNP as does farming; and research and development by itself equals farming. The health sciences relate to all three of these endeavors: to research and development, to health care and to education. And so, while the "golden century" may be behind us for higher education as a whole, I would like to suggest that there will be some golden decades ahead for the health sciences and the health professions; golden decades in terms of the opportunities to do more and more for the American people. The health sciences are not only more central to the welfare of our people as a whole but also more central to the conduct of higher education as our best contact with the people, our best service to the people. It may come to be that the greatest help that higher education will receive in this "time of troubles" will be from the success of the health professions.

Refer to: Physicians unions—Guilds (Report to the Council of the California Medical Association). Calif Med. 117:92-95, Sep 1972

Physician Unions—Guilds

Last November, a letter to the *American Medical News* from a San Francisco physician concluded with the statement: "I, for one, will continue to treat without charge my share of those who need my services and cannot pay, to teach without compensation the next generation of my fellow doctors, and to be the most conscientious doctor that circumstances will allow. But I'm for trading my badge of virtue for a union dues book."

In the months following this letter, the topic of unions for physicians has been a recurring theme in the press. An article in *Medical World News* offers one explanation of why some physicians are now interested in unionization. "In the seven years since the AMA lost its fight against Medicare, doctors who felt convinced that economic and political pressures on private practice would sooner or later become unbearable have groped for ways to organize and confront third parties with collective strength."

There is no doubt that physicians in various parts of the country are seeking ways and means to bolster their ability to resist unwanted government encroachments. There is also no doubt that the success of trade union members in improving their working conditions and wages through collective bargaining poses an attractive thought to physicians seeking an "escape" from political domination. A sampling of the articles in the press on this subject reveals a growing list of organizations entering this field. The April 3 issue of *American Medical News* reports that 30 Las Vegas physicians have formed the nation's first labor-affiliated union of physicians in private practice: the Nevada Physicians Union Local 676 of the Service Employees International Union, AFL-CIO. A recent edition of the *San Francisco Chronicle* notes that some 200 Bay Area physicians attended the first meeting of the Union of American Physicians in San Francisco.

The Wall Street Journal of March 6 discusses efforts by interns and residents in California and Chicago to form unions, noting that the Chicago group is considering affiliation with the AFL-CIO's Amalgamated Meat Cutters and Butcher Workmen of North America. A nationally chartered organization called the American Physician's Guild, with headquarters in Florida and branches in five states, the *American Medical News* reports, is urging a nationwide campaign to have physicians form "union-type" associations. The April 14 issue of *Medical World News* features an article titled "Doctors' New Bag Out West Is Unionism" and adds two additional organizations to those mentioned above, the San Antonio-based American Physicians Union and the Massachusetts Federation of Physicians.

Taken together, these and similar articles raise fundamental questions for the medical profession. They also present the reader with a veritable jungle of conflicting information and opinions. As a result, CMA feels that a thorough and factual examination of the physicians' union concept is called for.

What Exactly Is a "Union"?

With all the recent discussion of unions and "union-type" organizations for physicians, some particularly basic questions often have been overlooked: Exactly what constitutes a union? Who may form a union? What are a union's powers—both in regard to its members and in negotiating? In the United States, the answers to these questions have been spelled out in legislation and legal decisions over the years.

This report was adopted by the Council of the California Medical Association at its 585th Meeting, July 28, 1972, San Francisco.

Reprint requests to: Mr. Milton Krueger, Division of Professional and Public Relations, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

In law, a "union" or "trade union" is an association of (1) employees having a common employer; or (2) employees whose employers are engaged in a common industry; or (3) employees whose employers hire people in a specific trade or occupation. In each instance, the relationship of employer-employee must be involved. These organizations of employees have been given legal recognition to permit collective bargaining for the purpose of improving such terms and conditions of employment as wages, working environment and fringe benefits.

The weapons that unions have to enforce their bargaining demands are those of strike, threat of strike, or boycott. In connection with collective bargaining for improved terms of employment, the law sanctions strikes and, under some circumstances, boycott. Certain types of boycotts, such as secondary boycotts, are illegal.

What are a union's powers in regard to its members? In its 1959 decision in the case of *Chavez vs. Sargent*, the California Supreme Court quoted the following statement of the relationship between a union and its members:

"First, a union in collective bargaining acts as the representative of every worker within the bargaining unit. It speaks for him, makes choices of policies which vitally affect him, and negotiates a contract which binds him. His wages, his seniority, his holidays, and even his retirement are all governed by this contract which becomes the basic law of his working life. The union in bargaining helps make laws; in processing grievances acts to enforce those laws; and in settling grievances helps interpret and apply those laws. It is the worker's economic legislature, policeman, and judge. The union, in short, is the worker's industrial government. The union's power is the power to govern the working lives of those for whom it bargains, and like all governing power should be exercised democratically."

As this decision clearly states, a union exercises considerable power over the lives of its members. Furthermore, the courts have made it quite clear that members are committed to abide by union policies, whether they agree or not. A good illustration of this is the case of Cecil B. de Mille, who was ousted from a union for refusing to pay a $1 levy for political activities. As a matter of principle, de Mille fought the case all the way to the Supreme Court and lost.

Within the narrow framework allowed unions, these organizations of employees have been granted certain exemptions from the anti-trust laws.

What Do These Legal Points Mean for Physicians' Unions?

A recent letter to physicians calling upon them to form a "union" states: "It has been argued that by descending into the arena of collective bargaining we, as doctors of medicine, will lose our mantle of professionalism. We have only to look to our younger colleagues who, in spite of their as-yet untarnished idealism, have organized and won a decent wage for interns and house officers."

Elsewhere, the same letter states: "Without delving too deeply into the laws of economics it is easy to see that the physician has long ceased to be an independent entrepreneur and has in fact become an employee, either of insurance companies or of the government."

These statements raise a significant legal point and one basic to any discussion of physicians' unions. That is, a clear distinction exists—as far as labor law is concerned—between physicians who are employees and private-practice physicians who are self-employed.

For the purposes of clarification, "employer" might be defined generally as one who engages the services of another person or persons for wages or salary, "employee" as one who works for wages or salary in the service of an employer and "employer-employee relationship" as the basis under which the employer compensates the employee for his work. Physicians who are truly employees usually work for wages or salaries. Their time is not their own. By the terms of their employment, they are required to perform the employer's work during specified hours. While so engaged, these physicians are furthering the business of their employer.

Physicians who are compensated on a salaried basis may, like any other employees, form a union for the purpose of dealing with their employers. Several examples may be cited of existing unions which represent physicians employed by hospitals or by such industries as the railroads. When this type of group negotiates for wages, it is called collective bargaining, is exempted from anti-trust action and is legal.

However, the great majority of practicing physicians are defined as "self-employed" under the law. Deriving their income on a fee-for-service or capitation basis they are independent contractors and as such are subject to anti-trust laws. The Clayton Act, for example, grants statutory immunities to unions of employees but does not exempt non-employee organizations. If a non-employee organization negotiates as a group for payment, it is called price fixing and that is illegal.

Moreover, attorneys who have studied the question point out numerous legal decisions in which groups of essentially self-employed individuals were denied the immunities of union members. In one such case, in refusing to characterize the litigants as "employees," the U.S. Supreme Court pointed out that ". . . their desire is to continue to operate as independent businessmen, free from such controls as the employer might exercise."

The U.S. Supreme Court has made a similar observation regarding a physicians' organization —in this case the American Medical Association. The Court clearly distinguishes the physician members of AMA from "employees" and therefore rules them subject to Federal anti-trust laws:

"In truth, the petitioners represented physicians who desired that they and all others should practice independently on a fee-for-service basis where whatever arrangement for payment each had was a matter that lay between him and his patient in each individual case of service or treatment. The petitioners were not an association of employees in any proper sense of the term. They were an association of individual practitioners each exercising his calling as an independent unit."

The president of one "physicians' guild" is quoted by *Medical World News* as saying that because of the legal questions involved, his organization is not calling for the establishment of physicians' "unions" as such. "We are pushing for an organization capable of action in concert with and similar to the operation of unions," he said, adding that there is no reason why physicians cannot form associations that act like unions without calling themselves unions.

Here again, an important point might be raised: attorneys emphasize that the particular name chosen by such an organization makes no difference. It is the actions an organization takes that determines whether it is, in fact, a union.

The primary weapons in the arsenal of any trade union are activities which would quickly embroil any physicians' organization—whatever it chooses to call itself—in serious legal difficulties. Both criminal and civil prosecutions are possible under anti-trust laws. Criminal prosecutions can result in fines or imprisonment. Civil suits can lead to the award of damages—even treble damages—and highly restrictive injunctions. Furthermore, certain acts are held to be per se violations. Boycotting and pricefixing, essential tools for any trade union, are illegal if undertaken by anyone else. Trade union members, for example, can refuse to do business with those not meeting union terms. A concerted refusal to deal initiated by any other organization is a per se violation of anti-trust laws.

Other Questions Raised

Faced by encroaching and often unfair government controls, the prospect of collective bargaining—a successful tool for labor—naturally seems attractive to many physicians. However, today collective bargaining through any organized effort can only be effective if the bargainers are willing—and legally able—to utilize the weapons of strike or boycott, or both. Even disregarding legal considerations for a moment, several other important questions are raised regarding possible collective bargaining by physicians.

First, with whom would a physicians' union bargain? For any group of employees, the answer is simple: with the employer. But generally, physicians are not employees except to the extent that their patients might be seen as their "employers."

Would they bargain with government? While government certainly has become a major factor in medical care, the private sector has far from disappeared. Attempts at sweeping negotiations with government could easily act to encourage further government inroads into the medical care field. For physicians in private practice, there seems to be no counterpart to labor's "employer" with whom a physicians' union might bargain.

Next, against whom would a physicians' union strike (again ignoring legal considerations for a moment)? Against patients? Effective collective bargaining depends on muscle, and muscle would mean disregarding patient welfare to one degree or another. In this regard, even a strike against government, such as occurred in Quebec, essentially hurts the public rather than the politicians.

Obviously, the professional and ethical considerations of a strike by physicians are major considerations. The resort to striking—or withholding services or "collective non-practice" or any other euphemism for striking—is clearly in conflict with basic professional concepts. Certainly the majority of physicians recognize the public responsibilities of the profession and would find a strike unthinkable except in the most extreme desperation. In 1970, CMA's position on this subject was clearly stated by its House of Delegates: "that the physicians of California have one major responsibility and duty: the provision of medical care of the highest quality to all persons. That the California Medical Association believes that abandonment of patients through a concerted denial of service by physicians (strike) is an unacceptable method of solving problems or differences . . . The CMA urges that methods be sought by all members of the health team, including those administrative and political agencies which use the services of health workers, to achieve their desired objectives in an equitable, professional manner, protective of the health of all, without resorting to denial of service."

Another factor in unionization, "deprofessionalization," also is an important concern. CMA President Jean F. Crum puts it this way, "From my view, unionizing the medical profession would bring with it, in addition to a great many other disadvantages, the important deterrent that we would forever forfeit our professional status and jeopardize the dignity of our profession."

What effects could the existence of a powerful "union" of physicians produce with individual patients or the public generally? In a democracy, every effective organization must recognize that public understanding and support are essential if its objectives are to be achieved. Even discounting the possibility of strikes by doctors, there might well be difficulty in avoiding public opposition to physicians who band together for purely economic reasons. The importance of public opinion must not be ignored.

However distasteful it might be, the possibility of a strike can never be totally or realistically discounted for any organization negotiating for economic goals. What would be the financial effect for a physician and his family of a prolonged strike? Trade unions use the instrument of a "strike fund" to carry their members through the period of lost income. However, such a concept would be very difficult to apply for such professionals as physicians.

Another point is the effect that a physicians' union ultimately might have on the type of practice prevalent in this country. Certainly the very basis of the union concept—negotiation between employer and employee—would seem to favor modes of practice in which physicians are employees and to discourage individual private practice. The result could well be a radical shift in type of practice.

Legal and Professional Considerations in a Nutshell:

Unions are clearly defined under law and operate within a narrow framework. Employees (salary or wage earners) may unite to bargain collectively with their employers for improvement in the terms or conditions of their employment. In all cases, the relationship of employer-employee must be involved. It should also be noted that unions legally exercise considerable power over their memberships.

Any organization whose members are defined as self-employed does not fit the legal definition of a union. Therefore such an organization, whatever it calls itself, is not allowed the special statutory immunities granted trade unions and is not free to engage in collective bargaining. This is not to say that there is anything illegal in the formation of an organization for physicians in private practice which uses the name "union." However, attorneys point out that overwhelming legal problems will arise if the organizations acts —or even threatens to act—like a union. In addition, the matter of collective bargaining raises significant professional questions.

In short—because of the numerous legal and professional considerations—a physicians' union would be limited to the same activities presently being done by organized medicine. Furthermore, the danger exists that such a union would suffer from many of the disadvantages of the trade union, without the advantages. The primary responsibility of physicians remains to provide medical care of the highest quality to all persons.

PUBLIC HEALTH REPORT

Frederick B. Hodges, M.D., Director, State Department of Public Health

Mental Retardation Services

In past years a diagnosis of mental retardation often meant an automatic recommendation that the parents place their child in an institution. Now there are many alternatives available to families through the community care and service programs of California's Regional Centers for the mentally retarded.

Regional Centers, a potential resource for the personal physician, now provide community services throughout California. There are 13 such centers operated by voluntary community organizations and financed by public funds which are administered by the California Department of Public Health. They provide specialized diagnostic and counseling services for mentally retarded persons and their families, and are able to purchase a wide variety of services. Each center has a professional staff that includes physicians, psychologists, social workers, and other specialists to address the many problems associated with mental retardation. These staffs frequently work with personal physicians in establishing a definitive diagnosis and in helping a family understand what assistance is available to them.

Regional Centers maintain a life-long relationship with families of the mentally retarded, to enable them to cope with changing problems and to help the retarded individual to achieve his full potential. Center services may include diagnosis and counseling, guardianship, the purchase of medical, dental, day, or respite care, workshop or activity center services, and residential care. They are also responsible for determining whether an individual needs care in a state hospital.

In the six years that the Regional Center program has been in operation it has enabled many mentally retarded persons to maintain a satisfactory life within the community, at greater benefit to themselves, their family and their community, and at lower cost to the taxpayers.

By serving as advocates for the mentally retarded and their families, and helping the retarded to live as nearly normal lives as possible, Regional Centers are establishing realistic alternatives to institutionalization.

Further information on the Regional Center program is available from your local Regional Center or:

Bureau of Mental Retardation and
Disabilities Services
California Department of Public Health
2151 Berkeley Way
Berkeley, California 94704
Telephone: (415) 843-7900 Ext. 672

The 13 Regional Centers are:

Alta California Regional Center
1819 K Street
Sacramento, California 95814
(916) 444-7535
Serving Alpine, Amador, Calaveras, Colusa, El Dorado, Nevada, Placer, Sacramento, San Joaquin, Sierra, Stanislaus, Sutter, Tuolumne, Yolo and Yuba Counties.

Central Valley Regional Center
567 West Shaw Avenue, Suite B-160
Fresno, California 93704
(209) 227-3535
Serving Merced, Mariposa, Madera, Fresno, Kings and Tulare Counties.

Regional Center for the Mentally Retarded
Childrens Hospital of Los Angeles
P.O. Box 54700, Terminal Annex
Los Angeles, California 90054
(213) 663-3341
Serving Los Angeles County

Regional Center for the Mentally Retarded
Childrens Hospital of Orange County
1109 West La Veta Avenue
Orange, California 92668
(714) 633-6152
Serving Orange County.

Regional Center for the Mentally Retarded
Children's Health Center
8001 Frost Street
San Diego, California 92123
(714) 278-1500
Serving San Diego and Imperial Counties.

Far Northern Regional Center
P.O. Box 878
Redding, California 96001
(916) 243-4791
Serving Siskiyou, Modoc, Trinity, Shasta, Lassen, Tehama, Glenn, Butte and Plumas Counties.

Golden Gate Regional Center
346 Ninth Street
San Francisco, California 94103
(415) 864-0070
Serving Alameda, Contra Costa, Marin, San Francisco and San Mateo Counties.

Inland Counties Regional Center
788 North Arrowhead Avenue
San Bernardino, California 92401
(714) 888-6631
Serving San Bernardino, Riverside, Inyo and Mono Counties.

Kern County Regional Center
P.O. Box 459
2330 Truxtun Avenue
Bakersfield, California 93301
(805) 327-8531
Serving Kern County

Loma Prieta Regional Center
51 Notre Dame Street
San Jose, California 95113
(408) 275-8590
Serving Santa Clara, San Benito, Monterey and Santa Cruz Counties.

North Bay Regional Center
1220 Clay Street
Napa, California 94558
(707) 255-1282
Serving Sonoma, Solano and Napa Counties.

North Coast Regional Center
413 North State Street
Ukiah, California 95482
(707) 462-3832
Serving Humboldt, Del Norte, Mendocino and Lake Counties.

Tri-Counties Regional Center
22 West Micheltorena
Santa Barbara, California 93101
(805) 963-6717
Serving Santa Barbara, San Luis Obispo and Ventura Counties.

STEROID WEANING PERIOD

After patients stop long-term corticosteroid therapy, it generally takes about six months for the adrenal-pituitary axis to revert to normal sufficiently to handle all stressful situations. You have to keep this in mind. If a patient needs surgery, even three or four months after steroid therapy has been withdrawn completely, he should probably get supplemental steroids.

—MANUEL TZAGOURNIS, M.D., Columbus, Ohio
Extracted from *Audio-Digest Ophthalmology*, Vol. 9, No. 11, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

In Memoriam

Carter, Thomas Wendell, Hayward. Died June 19, 1972 in Hayward, aged 45. Graduate of Wayne University College of Medicine, Detroit, 1952. Licensed in California in 1954. Doctor Carter was a member of the Alameda-Contra Costa County Medical Association.

⁂

Carver, Cyril Ellis, Pasadena. Died June 27, 1972 in Pasadena of cerebral hemorrhage, aged 75. Graduate of the University of Alberta Faculty of Medicine, Edmonton, 1932. Licensed in California in 1943. Doctor Carver was a member of the Los Angeles County Medical Association.

⁂

Dallas, Donald Alexander, San Francisco. Died July 19, 1972 in Greenbrae, aged 73. Graduate of Stanford University School of Medicine Palo Alto-San Francisco, 1926. Licensed in California in 1926. Doctor Dallas was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Furlong, Robert M., San Rafael. Died July 18, 1972 in San Rafael, aged 82. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1917. Licensed in California in 1920. Doctor Furlong was a member of the Marin Medical Society.

⁂

Herzer, Fred E., Sr., Hilmar. Died July 4, 1972 in Modesto, aged 83. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1914. Licensed in California in 1914. Doctor Herzer was a member of the Merced-Mariposa Medical Society.

⁂

Hoover, James Nelles, Long Beach. Died June 29, 1972 in Long Beach of gastroduodenal hemorrhage, aged 85. Graduate of the University of Toronto Faculty of Medicine, Toronto, Ontario, 1923. Licensed in California in 1924. Doctor Hoover was a member of the California Medical Association.

⁂

Jones, Earl David, Stockton. Died February 16, 1972 in Stockton, aged 56. Graduate of St. Louis University School of Medicine, 1951. Licensed in California in 1952. Doctor Jones was a member of the San Joaquin County Medical Society.

⁂

Kelley, Edwin Hal, Roseville. Died March 31, 1972 in Roseville of widespread carcinoma, aged 74. Graduate of Northwestern University Medical School, Chicago, 1934. Licensed in California in 1935. Doctor Kelley was a member of the Placer-Nevada County Medical Society.

Klapper, Stephen Warren, San Jose. Died July 15, 1972 in San Jose, aged 36. Graduate of University of Michigan Medical School, Ann Arbor, 1963. Licensed in California in 1968. Doctor Klapper was a member of the Santa Clara County Medical Society.

⁂

Mansell, Denny H., Jr., Quincy. Was killed May 15, 1972 in an airplane crash, aged 53. Graduate of Creighton University School of Medicine, Omaha, 1945. Licensed in California in 1945. Doctor Mansell was a member of the Lassen-Plumas-Modoc-Sierra County Medical Society.

⁂

McGowan, James P., La Jolla. Died July 6, 1972 in La Jolla, aged 74. Graduate of Creighton University School of Medicine, Omaha, 1927. Licensed in California in 1945. Doctor McGowan was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

Sheldon, Francis Baldwin, Stockton. Died June 29, 1972 in Stockton of heart disease, aged 87. Graduate of Kansas Medical College, Topeka, 1910. Licensed in California in 1919. Doctor Sheldon was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

⁂

Tarr, Earl Mendum, La Canada. Died July 4, 1972 in La Canada of congestive failure, chronic hypoxemia, aged 83. Graduate of the University of Louisville School of Medicine, Louisville, Kentucky, 1915. Licensed in California in 1922. Doctor Tarr was a member of the Los Angeles County Medical Association.

⁂

Taylor, Edwin Addison, La Jolla. Died July 14, 1972 in Laguna Beach of heart disease, aged 58. Graduate of College of Medical Evangelists, Loma Linda-Los Angeles, 1944. Licensed in California in 1944. Doctor Taylor was a member of the San Diego County Medical Society.

⁂

Wilcox, Alex Brooke, Coarsegold. Died June 30, 1972 in Fresno, aged 56. Graduate of College of Osteopathic Physicians and Surgeons, Los Angeles, 1940. Licensed in California in 1940. M.D. degree from California College of Medicine, 1962. Doctor Wilcox was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associated member of the American Medical Association.

Refer to: Lewis AJ, Ailshie G, Criley JM: Pre-hospital cardiac care in a paramedical mobile intensive care unit. Calif Med 117:1-8, Oct 1972

California Medicine
THE WESTERN JOURNAL OF MEDICINE

Pre-Hospital Cardiac Care in a Paramedical Mobile Intensive Care Unit

A. James Lewis, m.d., Gaylord Ailshie, lt col, usar (ret)
and J. Michael Criley, m.d., *Torrance*

The high mortality in the early phase of myocardial infarction has prompted the development of many programs of pre-hospital coronary care. The ultimate result has been the "Coronary Care Unit on Wheels" staffed by registered nurses or physicians. Many of these units have not lived up to expectations, and have suffered from high initial and maintenance costs and under-utilization.

A pilot program has been developed at Harbor General Hospital which utilizes existing emergency paramedical manpower and resources, upgraded by specialized training and the use of drugs and portable electronic equipment. The aim of this program was to develop a Mobile Intensive Care Unit (MICU) which would be capable of responding to a wide spectrum of medical emergencies under the remote supervision of a physician utilizing radio-telemetry. Heavy emphasis was placed on the recognition and treatment of cardiopulmonary emergencies, so that pre-hospital cardiac care could be performed expeditiously.

The Training Program

Personnel. In the City and County of Los Angeles, the initial response to medical emergencies is the primary responsibility of the fire departments. The Los Angeles City Fire Department maintains a Rescue Ambulance Service, while the Los Angeles County Fire Department maintains a Fire Rescue Service which dispatches men and equipment to the scene of a potential emergency, but depends on contract or private ambulances for patient transportation. In preparation for Fire Rescue and Rescue Ambulance Service, the firemen receive advanced first-aid training in fire department training facilities.

Eighteen volunteers, twelve from the county and six from the city fire departments, were accepted in the pilot training program in 1969. These men had an average of two years' experience in fire rescue work, but had no previous medical training beyond advanced first-aid. Seventeen of them satisfactorily completed training.

Training. The pilot group of 18 men received 180 hours of classroom, laboratory and clinical instruction, followed by six to nine months of "internship" on a hospital-based MICU vehicle accompanied by a cardiac care unit nurse. Subsequent groups of trainees have received more than 300 hours of training, consisting of classroom and laboratory instruction and direct clinical experience (Table 1). A core faculty, based at the Paramedic Training Facility at Harbor General Hospital, participates in the training of each team. This faculty is supplemented by faculty from the base station hospital to which the team will be assigned.

The basic didactic phase of training (Table 1) takes two months and consists of both cardiac and non-cardiac subjects. The paramedic must be familiar with basic anatomy, physiology and the handling of a wide variety of medical emergencies. He is required to recognize cardiac arrhythmias, abnormal electrocardiographic com-

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Submitted October 4, 1971.

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TABLE 1.—*Paramedic Curriculum*

DIDACTIC PHASE

Topic	*Time*		
A. *Basic Subjects*			36 hrs
1. Medical Terminology		6 hrs	
2. Anatomy and physiology		30 hrs	
B. *Non-Cardiac Subjects*			76½ hrs
1. Medical		43 hrs	
History and physical exam	6 hrs		
Basic principles of pharmacology	9 hrs		
Common medical emergencies	6 hrs		
The unconscious patient	1½ hrs		
Shock	1½ hrs		
Hemorrhage	3 hrs		
Respiratory problems	3 hrs		
Pediatric emergencies	1½ hrs		
Psychiatric emergencies	1½ hrs		
Drug abuse	3 hrs		
Alcoholism	1½ hrs		
The stroke patient	1½ hrs		
Diabetes	1½ hrs		
Renal diseases	1 hr		
Legal aspects of emergency care	1½ hrs		
2. Surgical		10½ hrs	
Wounds	3 hrs		
Fractures	1½ hrs		
Burns	1½ hrs		
Head injuries	1½ hrs		
Emergency childbirth	3 hrs		
3. Special Techniques		23 hrs	
Venipuncture (lecture, demonstration)	7½ hrs		
Aseptic procedures	3 hrs		
Nasogastric intubation	1½ hrs		
Rotating tourniquets	1½ hrs		
Use of ventilation equipment	2 hrs		
Use and maintenance of MICU equipment	6 hrs		
Tracheal suction	1½ hrs		
C. *Cardiac Subjects*			55½ hrs
Normal heart	1½ hrs		
Abnormal heart	3 hrs		
Introduction to EKG	7½ hrs		
Arrhythmias	13½ hrs		
Cardiovascular drugs	12 hrs		
Causes of chest pain	1½ hrs		
Coronary heart disease	6 hrs		
Cardiogenic shock and syncope	3 hrs		
Congestive heart failure	1½ hrs		
Cardiopulmonary resuscitation and defibrillation	6 hrs		
D. *Miscellaneous*			37½ hrs
Orientations			
Reviews and practical exercises			
Quizzes			
Examinations			
Total Number of Hours of Didactic Instruction—			205½ hrs (2 mos)

CLINICAL EXPERIENCE

Type of Experience	*Time*
A. Clinical experience in hospital	136 hrs*
Intensive care units	
Emergency room	
Obstetrics	
I.V. team	
Cardiac diagnostic procedures	
Outpatient clinic	
B. "Internship" on hospital-based MICU	3 mos*
*These two phases run concurrently	
Total Duration of Course—	5 mos

plexes (bundle branch block, ischemia, infarction patterns and the like), and to be familiar with the apropriate therapy, including drug dosage and route of administration. He then must pass a written examination covering these subjects.

Following completion of the basic phase of training, a three-month "internship" is served. This consists of clinical experience in the hospital, and of answering emergency calls on the hospital-based MICU under the supervision of an experienced, certified MICU paramedic. Certification, under the Wedworth-Townsend Paramedic Act (see below) is performed by the Director of Hospitals after satisfactory completion of the five-month course.

Legal Aspects

In July 1970, the Wedworth-Townsend Paramedic Act (Article 3, Chapter 2.5, Division 2 of the California Health and Safety Code) was approved by the California State Legislature and signed by the Governor. This act was amended in June 1971 (Assembly Bill 492). Under the terms of the amended legislation, any hospital operated by or contracting with a county in the State of California may conduct a pilot program utilizing mobile intensive care paramedics for the delivery of emergency health care at the scene of an emergency, during transport to the hospital, and while in the hospital emergency department.

These MICU paramedics must have completed a minimum of 290 hours of training, including but not limited to experience in a Cardiac Care Unit and an emergency vehicle.

The Wedworth-Townsend Act contains several unique features. It authorizes a paramedic to institute cardiopulmonary resuscitation (CPR) and to defibrillate a pulseless, non-breathing patient

TABLE 2.—*Paramedic Team Configurations*

MICU Team	*Location*	*Vehicle*	*Comments*
Station 59 L.A. Co. F.D.	Fire station on hospital grounds	Station wagon	Hospital-based training unit. Paramedics maintain close contact with physicians and nurses. Paramedics work in CCU and Emergency Room between calls. Requires additional manpower from Fire Dept. Utilizes private or contract ambulance for patient transport.
Station 36 L.A. Co. F.D.	Fire station 1 mile from hospital	Utility truck	Upgraded Fire Rescue Service, requiring no additional manpower or vehicles. Unit responds to all emergency calls and fires. Unit carries equipment for extrication of victims from vehicular accidents, burning buildings, cliff rescues, etc. Utilizes private or contract ambulance for patient transport.
Station 53 L.A. F.D.	Fire station 10 miles from hospital	Rescue Ambulance	Upgraded Rescue Ambulance Service, requiring no additional manpower or vehicles. Unit responds to all emergency calls. Transports patient —not dependent on private ambulances.

without the order of a physician. This provision was made to permit immediate therapy in an otherwise fatal emergency, and to circumvent any time delays which may be encountered in reaching a physician. The institution of any other specific therapy must be under the authorization of a physician or certified MICU nurse,* and this authorization is valid as long as voice contact or a telemetered electrocardiogram is monitored by the physician or MICU nurse. The legislation permits the perenterel injection of six classes of drugs: antiarrhythmic agents, vagolytic agents, chronotropic agents, analgesic agents, alkalinizing agents, and vasopressor agents.

The physician and MICU nurse are exempted from liability for civil damages resulting from issuing instructions to a paramedic, as long as these instructions are given in good faith. The paramedics are similarly exempted from liability under separate legislation (California Vehicle Code, Chapter 934, Section 165.5).

Operation of MICU Teams

Three MICU paramedic teams currently operate from a base station at Harbor General Hospital. Although each of these teams received similar training and carries the same drugs and portable equipment, there are major differences in vehicles and modes of operation (Table 2).

Squad 59 is a Los Angeles County rescue unit operating from a small fire station on the Harbor General Hospital Grounds, which utilizes a station wagon carrying battery-powered portable equipment and drugs (Table 3). The six men work in two man shifts, 24 hours on, 48 hours off. They sleep and eat on the hospital grounds, and spend time between calls in the Cardiac Care Unit (CCU) and Emergency Room. These men wear white coats, are identified as "MICU Paramedics" with name badges, and are permitted to participate in many clinical activities in the hospital. They are permitted to assist the CCU nurses, record electrocardiograms, initiate intravenous infusions, perform CPR and countershock therapy and the like.

This unit is used as a training facility for paramedic trainees as well as experienced MICU paramedics for "refresher" training. Squad 59 responds to all rescue calls received from the fire rescue dispatch operator, and the men can be reached by "hot line" telephones in the CCU and fire station, by hospital pages, or via portable hand-carried radios. Their rescue response area consists of 59 square miles and overlaps the Squad 36 (see below) area. They may perform as a back-up unit for Squad 36.

Squad 36 is a Los Angeles rescue unit based at a fire station one mile from Harbor General Hospital and has a response area of 38 square miles. The six men work in two man shifts, sleep and eat at the fire station, and wear Fire Department uniforms. They respond to all fires as rescue paramedics, as well as to all rescue calls relayed by the dispatch center. Their vehicle is a standard fire department utility truck, equipped with cliff rescue gear, extrication tools and the

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*A certified MICU nurse is a registered nurse who has been certified by the appropriate county official as qualified in emergency cardiac care. She can perform the same functions as the base station physician.

TABLE 3.—MICU *Portable Equipment*

	Approximate Cost
1. EKG oscilloscope, battery powered	$ 950.00
2. Portable transceiver with EKG amplifier and modulator	3,200.00
3. D.C. defibrillator, battery-powered	1,750.00
4. Inhalation equipment	
Ambu bag	
Elder valve	
Oxygen	
Airways	
5. Aspirator, battery-powered	175.00
6. Drugs	
Vasoactive: norepinephrine, metaraminol, epinephrine, isosorbide dinitrate, glyceryl trinitrate, isoproterenol	
Chronotropic: isoproterenol	
Vagolytic agents: atropine	
Anti-arrhythmic: lidocaine	
Intravenous solutions: 5% dextrose, normal saline, Ringer's lactate, dextran	
Analgesics: morphine, pentazocine (Talwin®)	
Antidotes: 50% glucose, nalline	
Electrolyte concentrates: calcium chloride, sodium bicarbonate	
Miscellaneous: furosemide, benedryl, syrup of ipecac	
Sedatives, anti-convulsants: phenobarbital, diazepam (Valium®)	
7. Miscellaneous	
Stethoscope	
Sphygmomanometer	
Splints-vacuum type	
Obstetrical equipment	
BASE STATION (HOSPITAL) EQUIPMENT	
1. Base station transceiver with duplexer and antenna	2,300.00
2. Cassette tape recorder	100.00
3. Strip chart recorder	500.00
4. Demodulator	200.00

like, in addition to the portable MICU equipment. Neither Squad 59 nor Squad 36 transports patients to the hospital. A private or contract ambulance is called, and if indicated by the emergency or requested by the base station physician, a paramedic with portable equipment accompanies the patient in the ambulance to the hospital.

Rescue Ambulance 53 is a Los Angeles City Fire Department unit located about ten miles from Harbor General Hospital. It has a response area of 30 square miles. The men wear Fire Department uniforms, and they eat and sleep at the fire station. They respond to all emergency calls from the dispatcher, and transport the patient to the hospital in their vehicle.

The Base Station (Chart 1) for these three units is at Harbor General Hospital, and calls are received at a console on the Cardiac Care Unit consisting of a transceiver, demodulator (to convert tone signal to electrocardiogram), oscilloscope, strip chart writer, and cassette tape recorder. Each incoming call from a paramedic team is received by an intern or resident physician and recorded on cassette tape for later review by a staff physician. The electrocardiogram (EKG) is received as a frequency modulated (FM) tone signal which is recorded on cassette tape and can be displayed on the oscilloscope and recorded on the strip chart recorder. The cassette tape can be replayed to review both the voice and electrocardiographic data at any future time. Only on rare occasions was the telemetered ECG not of diagnostic quality for the interpretation of arrhythmias. A common problem was distortion of the ST segment.

Typical Operation

A patient in distress may dial the Fire Rescue dispatch number directly, state the nature of the complaint and give his name, age and address. As the dispatcher does not attempt to categorize or screen calls, delays in dispatching paramedics to the scene are kept to a minimum. The average

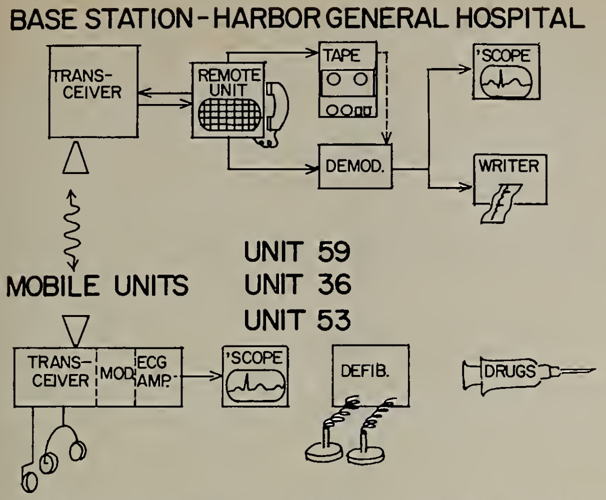

Chart 1.—Schematic diagram of base station and MICU (see text).

response time from the paramedics' receipt of the call from the dispatcher to arrival at the scene is 5.6 minutes.

Upon arrival at the scene, the paramedics briefly question and examine the patient and institute any necessary emergency resuscitative procedures. Electrocardiographic leads (self-adhering chest electrodes) are placed on the patient, if indicated, and contact is made by radio with the physician on the Cardiac Care Unit. The physician directs the course of treatment, such as starting intravenous infusion, drugs, or possibly countershock. As noted above, the paramedic may employ CPR and countershock before contacting the physician in dealing with pulseless, non-breathing patients.

Before transport, every attempt is made to stabilize the condition of the patient by countershock therapy, the administration of antiarrhythmic drugs and sodium bicarbonate, and the institution of antihypotensive medications as indicated. When stabilization has been reached (or reasonable attempts to bring it about have failed) the patient is transported to the hospital. Rapid transport with red light and siren is avoided when the patient has stable vital signs. If the patient has a cardiac problem, he is taken directly from the ambulance to the CCU, accompanied by the paramedics and their portable equipment. During transport, constant contact with the base station physician is maintained.

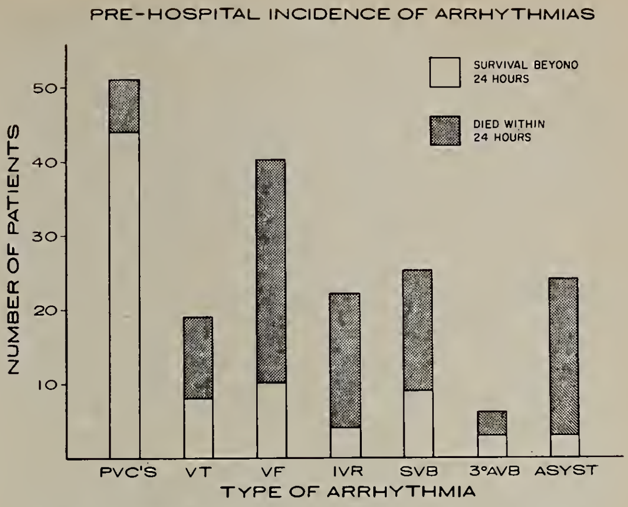

Chart 2.—Prehospital incidence of arrhythmias in 162 cardiac patients. More than one arrhythmia frequently occurred in a single patient. Mortality occurring within 24 hours of first contact with MICU is indicated by shaded bar.

PVC's = premature ventricular contractions; VT = ventricular tachycardia; VF = ventricular fibrillation; IVR = idioventricular rhythm; SVB = supraventricular bradycardia; 3° AVB = third degree atrioventricular block; asyst = asystole.

Most patients are transported to Harbor General Hospital, but they may request to be taken to a private hospital, in which case the base station physician calls the hospital to inform the physician or nurse on duty in the emergency room. If possible, the patient's private physician is contacted also. In cases of obvious cardiac distress (that is, suspected myocardial infarction, significant arrhythmias, hypotension and the like) a direct admission to the CCU in the outside hospital is arranged.

Results

From December 1969 through July 1971 a total of 2270 patients were seen by the three MICU paramedic teams. A detailed analysis of the results obtained during the first year of operation (December 1969-November 1970) has been completed and will be the subject of a subsequent report. In brief, 843 patients were seen. Two hundred and fifty-five (30 percent) complained of symptoms of a potential cardiac nature and 162 (19 percent) were found to have definite cardiac disease. Hence, 681 (81 percent) had non-cardiac problems.

The types of arrhythmias seen in the 162 patients with cardiac disease, and the mortality associated with these arrhythmias, are presented in Chart 2. In most instances more than one type of arrhythmia was seen in a single patient. In

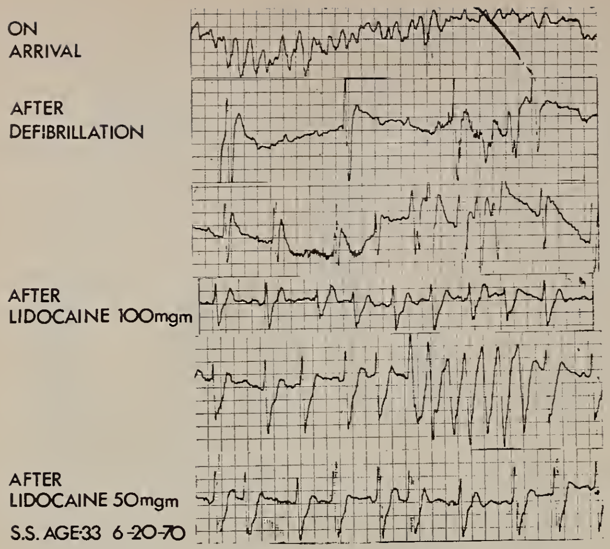

Chart 3.—Case 1. Electrocardiogram (lead II) received by radiotelemetry at base station (see text).

the majority of patients with ventricular fibrillation, ventricular tachycardia or asystole, the arrhythmia was present when the MICU team arrived. Eight of the ten surviving patients with ventricular fibrillation were in fibrillation at the time of first contact with the MICU. Twenty-five of the 30 patients with ventricular fibrillation who did not survive were in established ventricular fibrillation on first contact, while two were asystolic, two had bradycardia, and one had ventricular tachycardia which degenerated into ventricular fibrillation.

Reports of Cases

Case 1. (Chart 3.) A 33-year-old man who had had no previous cardiac symptoms, collapsed at home after prolonged chest pain. Ventricular fibrillation was initially detected by the MICU team. Following defibrillation, bradyarrhythmia was transiently present. Without specific drug therapy, supraventricular tachycardia with multiple premature ventricular contractions ensued. The ventricular ectopy was controlled with intravenous lidocaine. The patient was found to have an acute inferoposterior myocardial infarction. He made an uneventful recovery.

Case 2. (Chart 4.) A 48-year-old man without previous heart disease collapsed suddenly following a large steak dinner. Initial evaluation by the MICU paramedics showed absence of vital signs. The EKG revealed ventricular fibrillation. Following defibrillation, bradycardia developed. Atropine was administered intravenously, resulting in rapid atrial fibrillation with multiple premature ventricular contractions. The ventricular ectopy was controlled with intravenous lidocaine. Subsequent evaluation at the hospital revealed that the patient had aspirated a large quantity of meat. No EKG or enzyme evidence of myocardial infarction developed. The near fatal arrhythmia was secondary to hypoxia. He made an uneventful recovery.

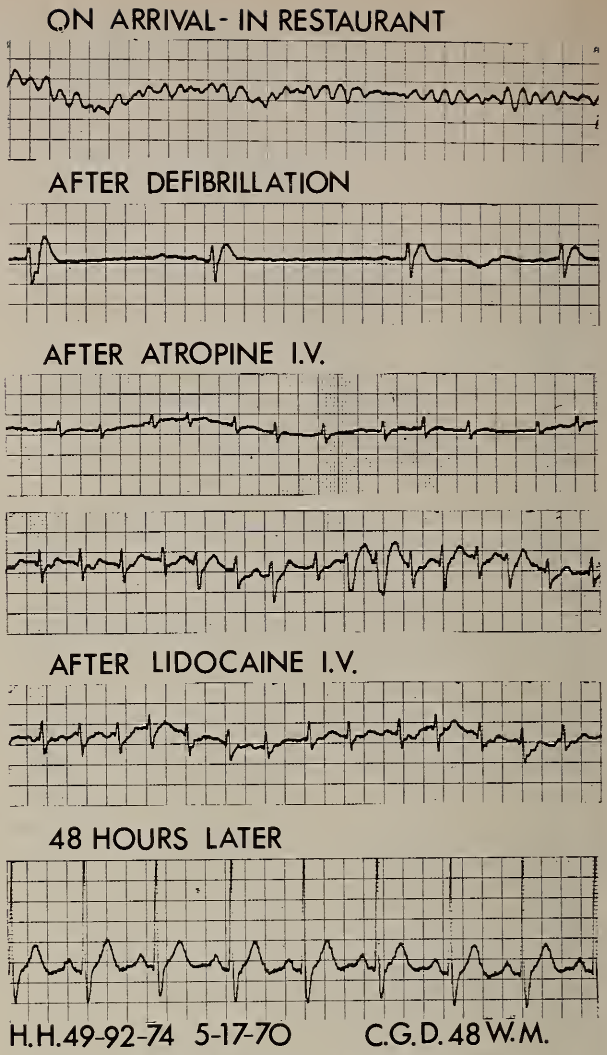

Chart 4.—Case 2. Electrocardiogram (lead II) received by radiotelemetry at base station (upper five panels), and 48 hours later (lower panel) while in hospital (see text).

Discussion

The prevention or reversal of "sudden death" by MICU paramedics has been demonstrated. As illustrated in the case reports, not always in reversible "sudden death" situations is coronary artery disease the culprit, although statistically it is the leading single cause of death in the United States.[1] Approximately 60 percent of myocardial infarction deaths occur before the patient can reach a hospital—usually within the first few hours after the onset of symptoms.[2,3] The majority of these deaths are probably the result of ventricular fibrillation, which occurs soon after the onset of symptoms.

To prevent or reverse the sudden cardiac death, adequately trained and equipped rescue teams must be available and capable of immediate response. It was felt that the shortage of physicians and nurses necessitated the use of paramedical personnel, and that utilization of the existing emergency manpower resources was preferable to development of a new system.

Pantridge, in Belfast, had already demonstrated the great potential for the physician-nurse "flying squad" approach to patients with myocardial infarction,[4] and Nagel and associates[5] had utilized firemen-paramedics to defibrillate patients under the remote supervision of a physician.

The Los Angeles program was the first to be legally authorized to administer parenteral medications. The case reports illustrate the necessity for using parenteral medications to supplement countershock in the treatment of arrhythmias. Two years' experience with this pilot program has provided certain guidelines for the training and utilization of county-wide and state-wide systems of enhanced emergency care.

Training must be comprehensive (see Table 1), since the only contact the remote physician has with the patient in the field is through the voice of the paramedic and the telemetered electrocardiogram. The latter may be badly distorted by motion or transmission artefact, which places a heavy emphasis on the clinical competence of the paramedic. Extensive clinical observation of patients with cardiopulmonary distress, experience in initiation of intravenous infusions, and learning to alleviate the patient's anxiety are beyond the realm of textbooks. Testing of the paramedics' competence and their continued reeducation are of paramount importance. At this time there are no state-wide curricula, examining boards or certifying agencies as there are for physicians, nurses and various therapists. The legislation designated "the county health officer or the director of hospitals designated by the board of supervisors" as the officer empowered to certify the training program. The Los Angeles pilot program has evolved considerably in the first two years of operation, and a minimum of 90 men in five additional classes will be trained under the current curriculum (Table 1). This curriculum could serve as a model for a state-wide program.

There is a large step between a pilot program and a county-wide or state-wide system of emergency medical care. The availability of paramedic manpower, hospitals in which to train them, and physicians to serve on the base station are three essential criteria for a program which can only be met with difficulty in many rural areas. From the point of view of cost-effectiveness, it is difficult to justify the existence of an emergency service devoted exclusively to the pre-hospital treatment of heart disease. Such units should be capable of responding to a wide variety of medical emergencies. The Los Angeles MICU teams are capable of handling a wide spectrum of emergency conditions ranging from childbirth and automobile accidents to an acute cardiac arrest. In addition, the diverse skills of the paramedics have been employed in the treatment of mass casualties resulting from fire or an earthquake.

Future evolution of the Los Angeles program will proceed along lines of increasing responsibility and training for the paramedic. We have been convinced of the necessity for training and authorization to perform endotracheal intubation. In Case 2 herein reported, the patient came very close to severe permanent brain damage due to persistent anoxia following otherwise successful resuscitation. We have also learned that the classes of drugs in the Wedworth-Townsend Act will have to be expanded to include diuretics and sedatives at the very least. A number of patients with severe pulmonary edema who did not improve after oxygen therapy and use of tourniquets were greatly helped by intravenous furosemide. Patients with seizures or who are combative have been effectively managed with diazepam. These drugs were used only when the nurses accompanied the paramedics in the first nine months of the program. They are now considered indispensable. It is hoped that the legislation will soon be amended to enlarge the list of parenteral medications, and to permit endotracheal intubation.

Summary

A mobile intensive care unit program utilizing extensively trained firemen-paramedics has been in operation in Los Angeles County since December 1969. Under terms of the Wedworth-Townsend Paramedic Act, properly trained and certified paramedics are permitted to initiate cardiopulmonary resuscitations and to defibrillate a pulseless, non-breathing patient. Upon the order of a physician who is in contact with the paramedics by radio, the paramedic may administer certain parenteral medications. A recent amendment to this law has permitted expansion of this program through California.

Experience with the program has indicated that a substantial number of needless deaths can be prevented. Since most of the emergency calls are non-cardiac, a categorical mobile cardiac care unit is not justified on the basis of cost-effectiveness.

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STEROID THERAPY CHECK-LIST

These are the general instructions I give for patients on steroid therapy, first as we watch them in the hospital on acute therapy and then for long-term use. We must get a chest x-ray and take precautions against infection. If the patient happens to have histoplasmosis or tuberculosis, putting him on steroids will aggravate the situation tremendously. One must get intermittent blood glucose levels and potassium levels to guard against the development of diabetes and hypokalemia. These are the two dangerous metabolic situations that can get a patient into real trouble. A low potassium level could kill the individual by an arrhythmia.

Antacids should be used to prevent or help prevent ulcer formation. Patients should be instructed in checking their urine for glucose. As much activity as possible should be prescribed for patients on corticosteroid therapy because this is the only way I know to prevent the osteoporosis and muscle wasting that this catabolic agent induces. The only physiologic counteraction against this is exercise, as far as I know.

Low-sodium diet will prevent some of the edema and swelling and hypertension that one sees with steroid therapy. Weight control is important because the appetite is almost invariably increased; and patients will tend to accumulate fat rather than muscle. The family should be made aware of and watch for mental changes because psychoses and nervous and mental breakdowns are a rather common problem. Patients should wear a Medic Alert identification bracelet because if they happen to get into an accident they must be given supplemental steroids. They should increase the dose for stressful events. They should be taught that when they have an infection or something happens to them they ought to take more steroids.

—Manuel Tzagournis, m.d., Columbus, Ohio

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Refer to: Hopkins GB, Tullis RH: Adenoid cystic carcinoma of the breast. Calif Med 117:9-11, Oct 1972

Adenoid Cystic Carcinoma of the Breast

G. Bruce Hopkins, m.d., and Richard H. Tullis, m.d., *La Jolla*

■ *Adenoid cystic carcinomas of breast are rarely recorded tumors affording an excellent prognosis. This present report documents three new cases and reviews the literature. Histologic features distinguishing it from cribriform intraductal carcinoma are emphasized.*

Adenoid cystic carcinomas are well-differentiated tumors of a singular morphologic pattern arising principally in salivary glands, tracheobronchial tree, nasopharynx, sinuses and uterine cervix. When they begin at those sites recurrence and metastasis are frequent and the prognosis is poor.[1] In sharp contrast, only four of the 49 adenoid cystic carcinomas reported as arising *de novo* in breast have recurred following excision.

This present report documents three additional cases of mammary adenoid cystic carcinoma and reviews the pertinent literature. Histologic features distinguishing it from cribriform intraductal carcinoma are emphasized.

Methods and Materials

From January 1958 to December 1971, 910 carcinomas of the breast were surgically excised at Scripps Hospital. These tumors were critically reviewed and three cases of adenoid cystic carcinoma were found. Some tumors that originally had been classified as adenoid cystic carcinomas were reclassified as cribriform ductal carcinomas and excluded from the study. Lesions in which other histologic patterns were admixed with the adenoid cystic pattern were also excluded.

Hematoxylin and eosin stains were routinely employed in the study of these tumors. In selected instances, periodic acid-Schiff, mucicarmine and phosphotungstic acid hematoxylin stains were also employed.

Clinical Findings

The salient clinical features of these new cases are summarized in Table 1. The ages of the patients at the time of diagnosis ranged from 33 to 69 years. The duration of symptoms before they sought medical advice was three to five months.

The tumor was present in the right breast of each patient. In two cases it was beneath or adjacent to the areolar area. The tumors were single, well-defined, movable and tender. Skin retraction or discharge was not present. Mammograms were considered suspicious of carcinoma in two of the three cases.

Radical mastectomy was done in all three cases. In one the tumor was associated with sclerosing adenosis and was not recognized at frozen section. When the lesion was noted on subsequent examination of the permanent sections, a second operation was done. The diagnosis of adenoid cystic carcinoma was suspected but not established at frozen section in the other two cases. Lymph node metastasis had not occurred in any case.

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Submitted February 25, 1972.

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TABLE 1.—*Data on Three Cases of Adenoid Cystic Carcinoma of the Breast Seen at Scripps Memorial Hospital*

	Age	*Breast Involved*	*Tumor Location and Size*	*Signs and Symptoms*	*Operation*	*Follow-up*
1.	33	Right	Right upper quadrant, 1.8 cm. in diameter	Tender mass noted for 3 months	Radical Mastectomy	Alive and well, 13 yrs.
2.	45	Right	Periareolar; 3 cm. in diameter	Tender mass noted for 5 months	Radical Mastectomy	Alive and well, 2 yrs.
3.	53	Right	Subareolar; 2 cm. in diameter	Painless mass noted for 3 months	Radical Mastectomy	Alive and well, 9 yrs.

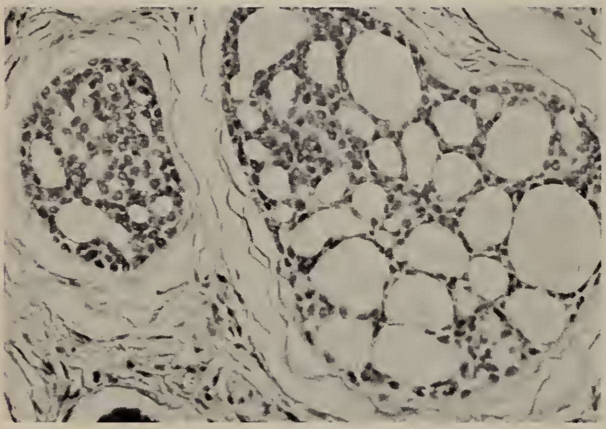

Figure 1.—Adenoid cystic carcinoma. Note the characteristic cylindromatous pattern (Hematoxylin and eosin x 100).

Each of the patients was alive and well at follow-up intervals of two to thirteen years.

Pathology

Grossly the tumors were well-defined, yellow-white, resilient, solid masses varying from 1.8 centimeters to 3.0 centimeters in maximum diameter.

The epithelial component consisted of islands or sheets of cells with cystic spaces forming the characteristic cylindromatous pattern (Figure 1). The cells were small, and cuboidal in shape, with scanty cytoplasm and regular nuclei. Acinar walls were generally two to four cell layers thick with the cells arrayed in a loose overlapping manner. Acinar spaces contained amorphous mucicarmine-positive material. Cellular atypia, necrosis or calcification were not present; mitosis was rarely seen. A biphasic cell population of myo-epithelial and luminal cells could be discerned in focal areas. The stromal component varied from densely hyalin to loosely areolar, the latter being more prominent about larger epithelial islands. Two of the tumors manifested neoplastic elements in perineural spaces; vascular or lymphatic involvement were not present.

General Discussion

Patients with adenoid cystic carcinoma have ranged in age from 31 to 80 years with an average of 56 years. The main presenting symptom has been a well-defined movable breast mass, frequently tender. Skin retraction has been recorded in five cases.[3] The duration of symptoms ranged from a few days to many years. No predilection for either breast and no bilateral lesions were recorded.

The tumors have been described as well-circumscribed, but non-encapsulated lesions ranging in size from 1 cm to 8 cm in greatest diameter, the majority being 3 cm or less. Six of the lesions were cystic, the remainder solid. Fixation of the chest wall and muscle invasion was present in one case.[4] Two were associated with contralateral ductal carcinomas.[2]

Cribriform intraductal carcinomas may mimic adenoid cystic tumors in microscopic appearance. As the former are more aggressive and have a far less favorable prognosis, it is important to distinguish between the two.

The cells of adenoid cystic carcinomas are arrayed in desultory fashion in acinar walls. Cell cytoplasm is scanty, nuclei are small and deeply staining, and mitosis is rarely seen. Conversely, cribriform intraductal cells display regular spacing in acinar walls. Cell cytoplasm is more abundant, nuclei are larger and more vesicular and mitoses frequent (Figure 2). Intraductal carcinomas lose the cribriform pattern with

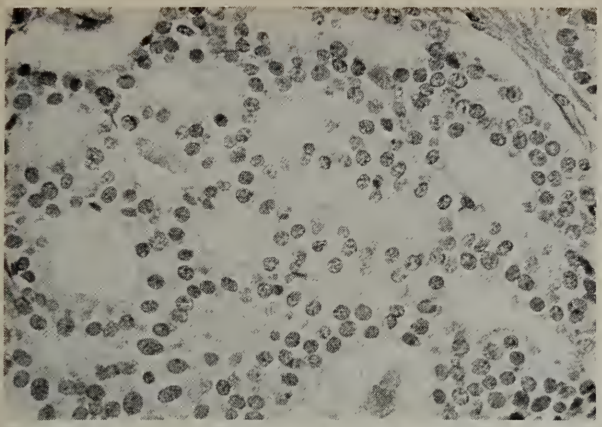

Figure 2.—Cribriform intraductal carcinoma. Note that the cells are uniformly arranged in acinar walls. Cell cytoplasm is more abundant, nuclei are larger and more vesicular (Hematoxylin and eosin x 250).

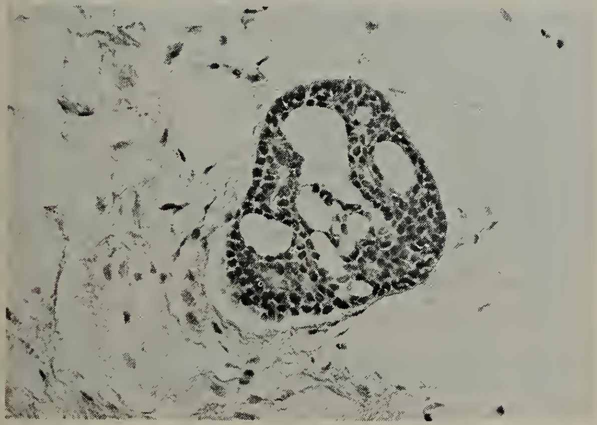

Figure 3.—Adipose infiltration by adenoid cystic carcinoma. Note that the cribriform pattern is maintained (Hematoxylin and eosin x 40).

stromal invasion; adenoid cystic tumors retain the acinar pattern even in areas of adipose infiltration (Figure 3).

A biphasic cell population of myo-epithelial cells and luminal cells may be seen in adenoid cystic tumors. The myo-epithelial cells are distinguished by smaller, more pyknotic nuclei and phosphotungstic acid hematoxylin-positive granules or fibrils in the cell cytoplasm.[2] Cribriform intraductal carcinomas are monophasic in appearance. Mucin production appears to be a more constant feature of adenoid cystic tumors.

The prognosis for these neoplasms appears excellent, as local recurrence has been noted in only four cases. The average time interval between original excision and recurrence was 11 years, with extremes of three years and 22 years. Three of the patients were initially treated by local excision; subsequent mastectomy proved curative.[1,4] In the fourth case a mastectomy was the original procedure, and removal of pectoral muscles and axillary contents was carried out when recurrence was noted seven years later. Eight years later a second recurrence in the chest wall necessitated removal of the ribs and soft tissues.[7] Two cases of pulmonary metastasis have been reported;[5,6] however, documentation in each is incomplete.

Occasionally the adenoid cystic pattern may be admixed with other histologic types of ductal carcinoma. If so, the prognosis is that of the other histologic type.[1]

Why adenoid cystic carcinomas in the breast should be less malignant than histologically identical tumors arising elsewhere remains obscure. The long intervals occurring between original resection and recurrence indicate a much slower growth rate. An equally important consideration is the relative ease with which total excision of breast tumors can be accomplished as compared with tumors in other sites.

Due to the paucity of reported cases, a standard method of treatment has not yet been validated. Wide local excision or simple mastectomy has been recommended;[1,2] however, practical considerations such as the rarity of the lesion, the difficulty of excluding cribriform ductal carcinoma on frozen section, and the need to examine many tissue sections to rule out an associated malignant lesion, quite possibly render this an academic point.

If the tumor is small, freely movable, located in a sub-areolar position and a definite diagnosis of adenoid cystic carcinoma is possible at frozen section, wide local excision would probably be adequate. If the diagnosis is only suspected, more extensive procedures could be delayed the few hours necessary for preparation and examination of high-quality permanent sections.

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Refer to: Adams RM: Shoe dermatitis. Calif Med 117:12-16, Oct 1972

Shoe Dermatitis

ROBERT M. ADAMS, M.D., *Palo Alto*

SOCKS AND THE LININGS OF SHOES were cited as causes of dermatitis by Duhring[1] in a textbook published in 1877, but it was not until after 1930, when the patch test became more widely used in clinical medicine, that dermatitis due to footwear was recognized with any frequency. Most of the reports of shoe dermatitis during the 1930's and early 1940's were concerned with allergy to the leather and dyes.[2-5] By 1950 rubber accelerator's and antioxidants had been added to the list of possible allergens, and increasing reports of allergic reaction to shoes appeared in the literature.[6,7] Following the contributions of Fisher,[8] Calnan,[9] Cronin,[10] Epstein,[11] and others, almost all dermatologists today recognize contact allergy to shoes as one of the most important causes of dermatitis of the feet. Many physicians who are not dermatologists, however, fail to make this diagnosis, chiefly because the possibility is not considered. But the disability which results, even with accurate diagnosis and the most careful treatment, often is prolonged and severe, and frequently occurs during the period of greatest physical activity and emotional turmoil, adolescence.

The wearing of shoes creates an environment for the feet which especially favors the development of contact dermatitis. For many hours daily we enclose our feet with leather, plastics, rubber, cloth, and adhesives containing hundreds of chemicals. Skin contact with these chemicals is maintained by the shoe's relative impermeability. The accumulation of sweat produces hydration of the stratum corneum and a pronounced increase in percutaneous absorption.[12] Samitz[13] and others have shown that sweat leaches out chrome from leather, and it is probable that other chemicals also are released by sweating. Heat, pressure, and friction accompanying movement and standing are additional factors which promote the development of sensitivity.

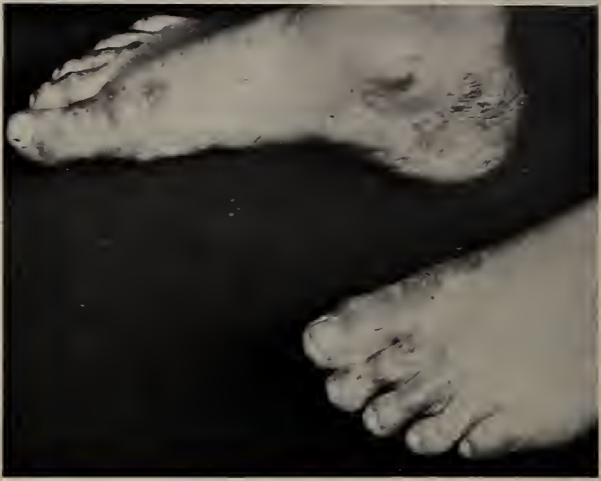

Figure 1.—Allergic contact dermatitis due to shoes in a 12-year-old boy. The condition had been incorrectly diagnosed and treated as "athlete's foot" for over four years. On patch testing the causative allergens were found to be mercaptobenzothiazole and p-phenylenediamine.

Why most people do not become allergic to their shoes can be explained in part by the small concentration and relatively low sensitizing index of most allergens in shoes. Also important deterrents are a microenvironment of the feet in which sweating and heat are relatively normal.

This report describes 35 patients with shoe dermatitis diagnosed and treated at the Palo Alto Medical Clinic between 1968 and 1971.

Clinical Appearance

The eruption may begin anywhere on the feet, but usually first appears on the dorsum of the great toes (Figure 1).[14] The heels, sides of the feet, and other areas of pressure and friction are also common sites. The plantar surfaces may be affected, but the interdigital spaces only in severe cases or in sandal dermatitis. The eruption is

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Submitted January 17, 1972.

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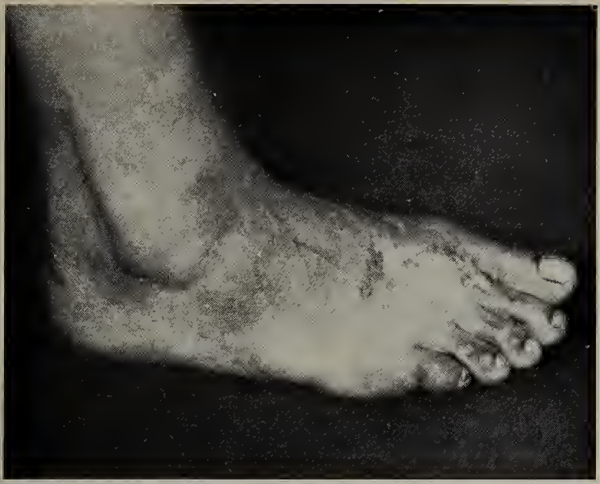

Figure 2.—Depigmentation of the dorsum of the feet due to monobenzylether of hydroquinone, used as an antioxidant in rubber. Patch tests with this chemical reproduced the condition shown. The resemblance to vitiligo is striking, and indeed the condition is often confused with it.

highly pruritic, eczematous, bilateral, and usually symmetrical. A history of increased sweating is almost always obtained, and some seasonal variation is usually noted. Persons of any age may be affected, but our series shows a preponderance under 20. Racial differences are not apparent. Rarely leucoderma is a late sequella (Figure 2), due to the depigmenting action of certain phenolics used as antioxidants in rubber, especially monobenzylether of hydroquinone.

Early in the course of the disease the eruption usually occurs only when a certain pair of shoes is worn, but later the condition becomes continuously present and very persistent. Occasionally the hands are also affected, either from handling the shoes, or from wearing rubber or leather gloves containing the same allergens as the shoes. The possibility of an "id-like" reaction on the fingers and hands must also be considered.[14] Secondary bacterial and fungal infections readily occur.

The design of the footwear determines to a large extent the appearance of the dermatitis. Sandals may cause an eruption at one or more of the spaces between toes and especially under straps over the instep and around the ankle. Dermatitis from sandals made from East Indian buffalo hide is usually abrupt in onset, especially after the sandals have become wet. Vesiculation resembling Rhus dermatitis regularly occurs (Figure 3) and extension up the ankles and calfs is characteristic.

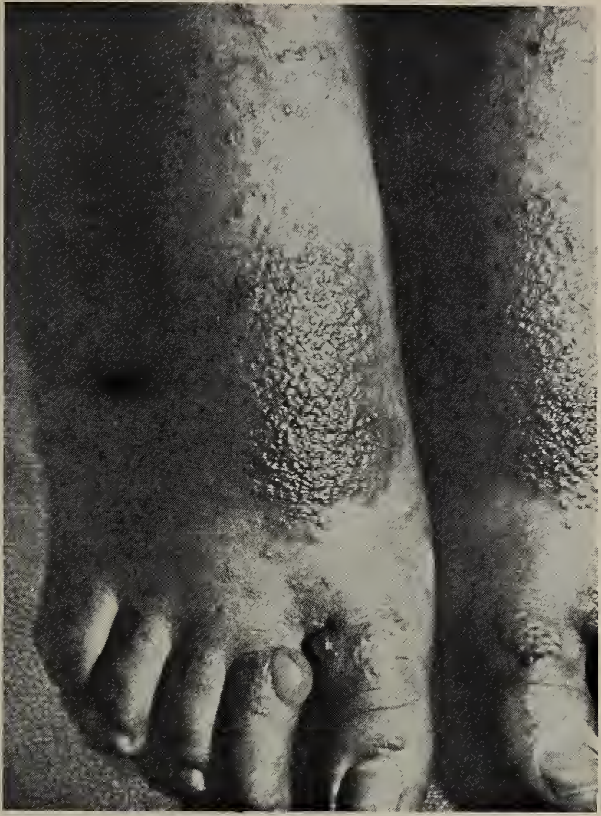

Figure 3.—Acute vesicular eruption from sandals made of East Indian buffalo hide. The dermatitis was extremely pruritic and vesicular and extended to the ankles and calfs. The causative allergen, probably a vegetable tanning agent, has not yet been discovered.

Stocking dermatitis outlines the shape of the stocking. With long women's stockings, popliteal fossae and inner thighs are affected. The causative agents are usually found to be dyes or the rubber elastic. Most stocking dyes are disperse-type azo dyes and some may cross-react with paraphenylenediamine.[15]

Differential Diagnosis

Shoe dermatitis may closely resemble several other conditions. Fungal infections are most commonly confused with it, sometimes for years,[16] and antifungal medications greatly aggravate the dermatitis. Atopic dermatitis, in young children especially, closely resembles the subacute or chronic stages of shoe dermatitis; and indeed the friction of stiff shoes may trigger the atopic condition. Also important to consider in the differential diagnosis are psoriasis and lichen planus.

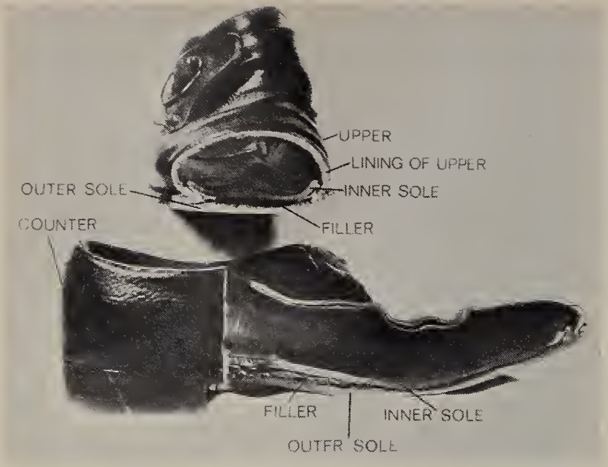

Figure 4.—Construction of a man's shoe.

TABLE 1.—*Chemicals Used in Patch Testing for Shoe Dermatitis**

LEATHER:

1. potassium dichromate, 0.5% aq.
2. formalin, 2% aq.
3. glutaraldehyde, 2% aq.
4. vegetable tans:
   quebracho, 1% aq.
   myrtan, 1% aq.
   spruce, 1% aq.
   chestnut, 1% aq.
   wattle, 1% aq.
   **sumac, 1% aq.

RUBBER:

1. mercaptobenzothiazole, 2% pet.
2. tetramethylthiuramdisulfide, 2% pet.
3. n-cyclohexylthiazylsulfenamide, 1% pet.
4. monobenzylether of hydroquinone, 1% pet.
5. 1, 3 diphenylguanidine, 1% pet.
6. p-phenylenediamine, 1% pet.
7. isopropylaminodiphenylamine, 0.1% pet.

DYES:

1. Bismarck brown, 5% aq.
2. p-phenylenediamine, 1% pet.
3. p-aminoazobenzene, 0.25% pet.

ADHESIVES:

1. p-tert-butylphenol formaldehyde resin, 5% pet.
2. acrylic monomer, 25% olive oil
3. rosin (colophony), 10% olive oil

ANTIMELDEW AGENTS:

1. phenylmercuric nitrate, 0.05% pet.
2. o-phenylphenol, 1% pet.
3. formaldehyde, 2% aq.

*Many of these materials are available from Karen Trolle-Lassen Laboratory for Dermatological Patch Tests, Høyrupsalle 1, 2900 Hellerup, Denmark.

**Should be used with caution in patients sensitive to the Rhus family of plants.

Causative Allergens and Construction of Shoes

The contact allergens found in shoes reflect the changing technologic trends in shoe manufacture. Once made almost exclusively of leather, footwear over the last 50 years has undergone many changes in composition. As might be expected, man-made plastic materials are gradually replacing leather and other natural products. For years, only chrome-tanned leather was used for shoe uppers, but recently much chrome-tanned leather is retanned with vegetable tans or synthetic tanning agents ("syntans") to achieve special qualities. The "box toe," also made exclusively from reclaimed rubber or nitrocellulose resins, is now increasingly constructed of newer plastic materials such as ionomers which are extruded between layers of cotton fabric. Most counters are still made of leather, but in many women's shoes polyethylene and fiberboard are used. Inner soles may be leather, vinyl, or even Teflon. Cork mixed with urethane plastic may be employed to provide a soft "cushion," and as a "filler" beneath the inner sole (Figure 4).

Although various parts of the shoes may be sewn together with nylon, polyethylene, or acrylic thread, adhesives are also used to prevent "squeaking." Most shoe adhesives are rubber-based or resins such as p-tert-butylphenol formaldehyde resin (CKM 1634, Union Carbide). Acrylic, polyvinyl and rosin-based resins are also used.

Hundreds of dyes are used and it is very difficult to learn which ones are used in a given shoe. Most tanneries identify dyes by trade mark or their popular names and only rarely by the official Color Index titles. Furthermore, leather dyeing is still more art than science, and the exact combinations of dye employed remain closely guarded secrets. Shoe dyes rarely cause dermatitis today anyway, unless the shoes have been re-dyed.[15] Bismarck brown, p-aminobenzene, and p-phenylenediamine have been recommended for patch testing. The latter is not used as such in shoe dyeing, but may cross-react with other related dyes.[15] It should be remembered, however, that several rubber antioxidants cross-react with p-phenylenediamine, and demonstration of sensitivity to p-phenylenediamine does not necessarily signify contact sensitivity to a dye.

Cloth linings and other parts of the shoe may contain anti-mildew agents such as phenylmercuric compounds and phenolic-type germicidal agents including phenylphenols, salicylanilides, and formaldehyde.

Patch Testing in Shoe Contact Dermatitis

The patch test is the most important diagnostic aid in the study of shoe dermatitis. The chemicals which may be used in patch testing are shown in Table 1. The first reading must not be done before 72 hours, and sometimes re-reading is necessary at 96 hours. The test patches are removed at 48 hours and each site circled with Dy-O-Derm stain (Owen Laboratories), to provide an identifying marker which will remain for three to four days.

One should also test with material from the suspected shoes. Scrapings should be taken from the box toe, inner sole, and heels in sufficient quantity to cover patches which have been previously moistened with warm water. Sometimes it is necessary to take the shoe apart and test with small squares of the individual layers, after splitting any thick pieces to avoid false-positive pressure reactions. When the offending shoes have been worn for a long time, each layer becomes impregnated with the various chemicals from other layers, and thus a positive patch test with a given section of the shoe does not necessarily mean the allergen originally was present at that site. Furthermore, because one cannot duplicate the sweating, heat and friction of actual use in the patch test, a negative result from testing with material from the shoe does not eliminate it as the cause of the eruption. A positive reaction to one or more of the known allergens in shoes is sufficient evidence for making a diagnosis of shoe dermatitis, unless the history and physical findings suggest otherwise.

Why is it necessary to test with the chemicals shown in Table 1 if the patient reacts positively to a test with the shoe itself? A positive reaction to a specific chemical tells the physician whether the allergen is in the rubber, leather, fabric lining, dyes, adhesives or a combination of these. This information is indispensible in planning treatment and in ordering hypoallergic shoes. A positive result from patch testing also emphasizes to the patient the real cause of his disease and usually induces much more cooperation during treatment, which unfortunately is frequently only partially successful.

Comment on 35 Cases

In 35 cases studied, there was an almost equal division between the sexes—18 males, 17 females. Race is not identified on PAMC charts, so racial variation cannot be shown, but other investigators have not demonstrated any differences.[17] The ages of our patients ranged from 7 to 65 but almost one-half were 20 years of age or under. The "big three" allergens were mercaptobenzothiazole, p-phenylenediamine and potassium dichromate, but it is noteworthy that two patients reacted to shoes alone and not to a specific chemical. Allergens were found in 30 shoes, four sandals and one boot. In 13 cases there was only one allergen, in eight cases two, and in eight others three. The number of patients reacting to each of the allergens listed was as follows: to mercaptobenzothiazole, 15; p-phenylenediamine, 13; potassium dichromate, 7; shoes or sandals only, 6; p-tert-butylphenol formaldehyde resin, 4; formalin, 3; tetramethylthiuram disulfide, 3; n-cyclohexylthiazyl-sulfenamide, 2; monobenzylether of hydroquinone, 2; diphenylguanidine, 2; Bismarck brown, 1. Four were sensitive to sandals alone and they showed positive reactions only to sandals made from East Indian buffalo hide, the allergens in which have not yet been identified.[18] In each of these patients, we tested with the vegetable tanning agents shown in Table 1 and no positive reactions occurred. P-tert-butylphenol formaldehyde resin, in our shoe test kit for only a short time, has already been responsible for eight positive reactions out of 98 tests. Four of these were from shoes. In comparison, from 167 tests with tetramethylthiuram disulfide we have recovered only seven positives, four of which were from shoes. While 13 of our patients had only one sensitivity, in 14 we demonstrated two or more. Frequently these patients described other situations in which dermatitis developed from contact with a totally different substance which was found on investigation to contain one of these chemicals.

Treatment

For adults and older adolescents hypoallergic shoes may be ordered from the Foot-So-Port Company.* Two types of shoes are currently available from this manufacturer: (1) Type A, in which the leather is vegetable tanned, the shoe containing no rubber or formaldehyde; (2) Type B, in which the leather is chrome-tanned, the shoe also containing no rubber or formaldehyde. This company also supplies samples of vegetable tanned leathers and other materials for patch testing. Many retail outlets are found throughout the country. Because these shoes must be made to order, six to eight weeks should be allowed for delivery. The price is higher than for ordinary shoes.

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*Foot-So-Port Shoe Company, Division of Musebeck Shoe Co., Forest and Westover, Oconomowoc, Wisconsin 53066.

Measures to control sweating may be very helpful to these patients. Application of Zeasorb powder (Stieffel®) once or twice daily, changing the socks two or three times a day, and the wearing of different shoes for work and home, help prevent dermatitis. A light application of a steroid-containing aerosol spray each morning is also useful.

Treatment of acute episodes does not differ from treatment of contact dermatitis on other parts of the body. Wet compresses with Burow's solution, application of steroid-containing lotions and creams, oral antihistamines, and occasional short courses of systemic steroids are usually very effective. Systemic antibiotics must be administered for secondary bacterial infection. Chronic lichenified dermatitis is best treated by application of steroid-containing creams under thin plastic film occlusion at night.

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CHANGE OF COMMAND FOR THE NEWBORN WITH HEMOLYTIC DISEASE

In an infant with hemolytic disease of the newborn, when does the obstetrician's responsibility end and the pediatrician's responsibility begin? A number of cases in litigation dealing with a hiatus between the responsibility of these two physicians.

Is it the obstetrician's duty to call in the pediatrician, and, if so, when does the obstetrician's responsibility end? At the time he makes the call? At the time the pediatrician is notified and says he will arrive? Or at the time the pediatrician actually arrives on the scene and begins his examination of the child? It is quite important to recognize, particularly on the part of the obstetrician, that his responsibility continues until the next man comes in and actually undertakes active diagnostic and therapeutic measures. It is not enough to just say to the nurse, "Have Dr. So and So come in and take over the care of the child," and then promptly forget or neglect that child. There may be a considerable period of time before the pediatrician arrives on the scene and during that period catastrophes can occur for which the obstetrician would still have responsibility.

—Don H. Mills, m.d., ll.b., Los Angeles

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Refer to: Benner EJ: Practical use of penicillin, cephalosporin and aminoglycoside antibiotics (Medical Progress) Calif Med 117:17-27, Oct 1972

Medical Progress

Practical Use of Penicillin, Cephalosporin and Aminoglycoside Antibiotics

E. JACK BENNER, M.D., *Davis*

THE USE OF ANTIMICROBIAL agents has increased steadily as the expertise of physicians and surgeons has prolonged survival of patients with many different diseases. The number of agents available is so large that a physician can skillfully use only a small portion of the total. It is the purpose of this article to highlight some important features of commonly used (and abused) antibiotics that, if used properly, should provide excellent therapy for the vast majority of infections encountered in the usual practice. No attempt will be made to be all inclusive. The guiding principles will be application of microbiologic and pharmacologic data to clinical situations to allow efficacious and safe therapy of the more common bacterial infections amenable to therapy with these groups of antimicrobial agents.

Oral penicillins and cephalosporins. Although there are many preparations available, only a few are required. The major requirement for oral therapy is that the antimicrobic provide serum antibacterial activity adequate to kill the usual pathogens in the diseases commonly treated with medicine by mouth. Therefore, in all but urinary tract infections, serum antibacterial activity and diffusion to body fluids and tissues are required. Table 1 summarizes the six oral agents considered most useful. Several simple principles will help in using these six agents.

Antibiotic susceptibility reports are not infallible. If any Staphylococcus aureus is reported susceptible, that is, sensitive, to one or more of the lactamase susceptible drugs such as benzylpenicillin (penicillin G), ampicillin, or phenoxymethyl penicillin (penicillin V), but intermediate or resistant to any other in this group of three, assume that the staphylococcus is penicillin resistant since the laboratory data is incongruous. These three drugs, benzylpenicillin, ampicillin and phenoxymethyl penicillin, are all easily destroyed by the lactamase(s) (penicillinase) produced by S. aureus. If there is an inconsistency in susceptibility to these drugs, then the test is in error. The use of cloxacillin or cephalexin, both of which are resistant to destruction by the staphylococcal lactamases, obviates this problem. In serious infections requiring long term or high dosage therapy, it may be necessary to demand repeat susceptibility tests to prove that the pathogen is incapable of producing penicillinase and, therefore, will be susceptible to benzylpenicillin, ampicillin or phenoxymethyl penicillin.

It is wasteful to perform disc susceptibility tests for these six antibiotics against Beta hemolytic Streptococcus pyogenes, Diplococcus pneumoniae, Neisseria gonorrheae, or Neisseria meningitidis, for all strains are susceptible. Some gonococci have slightly increased resistance against penicillins but this is not detectable by the disc test.

Influence of food on absorption. Benzylpenicillin must be given 30 minutes before meals for adequate absorption, even when trying to prevent recurrent attacks of rheumatic fever by eradicating Beta hemolytic streptococci from the throat. When given before meals it does provide serum levels adequate to eradicate Streptococcus pyo-

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TABLE 1.—*Facts about commonly used oral penicillins and cephalosporins.*

Drug	*Activity against penicillin-resistant Staphylococcus aureaus*	*Activity against Hemophilus spp*	*Ordering for maximum absorption*	*Effect of renal failure on dose schedule*	*Comments*
Benzylpenicillin (penicillin G)	None	Poor	30 minutes before meals and at bedtime.	Minimal	Inexpensive therapy of common infections.
Phenoxymethyl penicillin (Pen-Vee-Oral, V-Cillin, Pen-Vee, Compocillin-V, Betapen-VK, Compocillin-VK, Ledercillin-VK, Pen-Vee K, V-Cillin K)	None	Poor	Food reduces absorption some—best given before meals and at bedtime.	In severe oliguria, or anuria, reduce dose to q 12 hr.	Very reliable blood levels in most patients.
Ampicillin (Alpen, Amcill, Omnipen, Penbritin, Polycillin, Principen, Totacillin)	None	Most Active.	Food reduces absorption some—best given before meals and at bedtime.	Minimal	Agent of choice for *Hemophilus spp.*
Cloxacillin (Tegopen)	Active	Poor	Food reduces absorption some—best given before meals and at bedtime.	Same as Phenoxymethyl penicillin.	Preferred oral penicillin for staphylococcal infections.
Cephalexin (Keflex)	Active	Active	Food has little effect.	Regulate doses according to Table 2.	First alternate to the penicillins—especially for Staphylococcal infections.
Cephaloglycin (Kafocin)	Active*	Unknown*	Food has little effect.	Little effect.	*Use only for urinary system infections.

genes, susceptible strains of S. aureus and the pneumococcus. In addition, this provides high concentrations of benzylpenicillin in the urine which is usually effective in eradicating the common infections due to susceptible strains of Escherichia coli and Proteus mirabilis. Even the acid stable agents, such as cloxacillin, cephalexin, cephaloglycine and phenoxymethyl penicillin, provide higher serum antibacterial activity when given 30 minutes before meals and at bedtime, rather than four times a day or every 6 hours, since these orders usually result in the medicine's being given with or after meals.

Hemophilus. If Hemophilus spp. is the likely pathogen, ampicillin is the most effective agent, although cephalexin has been successful in most bronchitis and otitis infections reported in this country.

Cephaloglycine. This agent does not provide serum activity of an amount necessary to treat other than urinary tract infections.

Dose adjustments in renal failure. Adjustments of the size of the dose and the duration of the interval between doses can be used to prevent accumulation of antibiotics in patients with renal failure or to accomplish higher serum levels in patients with normal renal function. With drugs such as benzylpenicillin, cephalexin and phenoxymethyl penicillin, elimination is accomplished via the kidneys in a very rapid fashion. The serum half life (T ½) is very short in patients with normal or near normal renal function. Since the half life is prolonged when renal dysfunction is significant (clearance of creatinine less than 40 ml per minute per 1.73 square meters of body surface), elimination of the drug is less and the drug will accumulate in the serum if usual doses are given. Since elimination of the drug is determined by the half life at any given level of renal function, it was possible to develop a nomogram to provide a dose schedule in patients with renal failure.[1] This schedule provides therapeutic blood

TABLE 2.—***Doses of cephalexin to give 8 hourly for patients with renal failure. Load with 1 gram by mouth, then adjust dose according to clearance of creatinine value. (From Regamey C, Humair L: Postgrad Med J Suppl 47:69-78, 1971)***

Clearance of Creatinine (ml/min/1.7m²)	*Dose mg every 8 hours*
>40	500
40	approx 400
30	300-350
20	250
10	150
2 or less	50

(pulvules contain 250 or 500 mg; suspension contains 125 mg per ml)

levels without significant accumulation of the drug in the serum. Table 2 is a summary of the dosage recommended at 8 hourly intervals to provide near steady state serum activity of cephalexin. Similar reduction in dosage can be made for benzylpenicillin and phenoxymethyl penicillin.

Conversely, some diseases require amounts of antibiotic in the serum that are usually achieved only by the parenteral route. However it is extremely costly to keep patients in the hospital just to receive antibiotic by this route. Since accumulation will occur if an agent that inhibits elimination of the antibiotic is given at the same time interval between doses of antibiotic is shortened, it is possible to attain high serum levels by oral antibiotic dosage schedules. This is clearly demonstrated in Chart 1. This patient had a S. aureus adenitis and cellulitis. To provide high serum levels by oral administration the dosage interval was shortened and probenecid was used to prolong the T½ of cephalexin. As a result, serum levels of 40 to 60 μg per ml were achieved through most of the day and he was cured. A standard oral dosage regimen had allowed relapse of his infection when he was changed from parenteral to oral therapy. Similar results have been obtained in treating lung abscesses, osteomyelitis, and other staphylococcal infections with both cephalexin and phenoxymethyl penicillin.

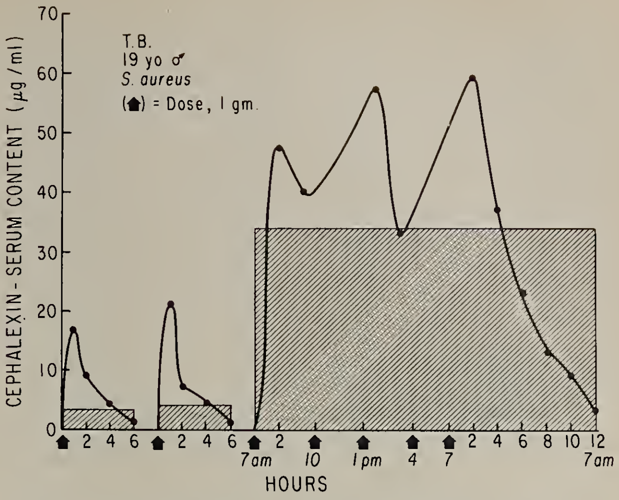

Chart 1.—Cephalexin content of serum increased to high levels by dosing every 3 hours and administering probenicid before doses compared to actual (solid lines) and average (hatched areas) serum activity during 6 hourly dose schedule.

Ampicillin is not a true "broad-spectrum" agent. Ampicillin is not effective against S. aureus strains that are resistant to penicillin G and is ineffective against a large percentage of strains of Gram-negative bacilli isolated from urine, wounds, and the bronchopulmonary tree. It is not significantly more active against E. coli or Proteus mirabilis (the commonest urinary tract infecting agents) than benzylpenicillin or phenoxymethyl penicillin. These facts, and the knowledge that peak serum levels usually do not exceed 3 to 4 μg per ml after an oral dose of 0.5 grams make it evident that there is little to support the use of ampicillin as a "broad spectrum" antibiotic.

Specific indications for its use relate to its efficacy against Hemophilus influenzae in upper respiratory infections in children and in adults with chronic bronchitis. The evidence that morbidity is decreased significantly when bacillary dysentery due to susceptible strains of shigella are treated with ampicillin[2] is convincing, and in addition carriers of Salmonella typhosa with a normal gallbladder can sometimes be cured of the carrier state with oral ampicillin.[3]

Most acute infections of the urinary tract can be treated with an oral penicillin or cephalosporin because of the high concentrations of antibiotic achieved in the urine. Although many strains of E. coli, P. mirabilis and enterococci recovered from patients with acute infections of the urinary system are resistant to 5-10 μg per ml of these antibiotics, 100 μg per ml kills nearly 100 percent of the strains recovered from patients who acquire their infection outside the hospital.[4] Standard doses (Chart 2) of benzylpenicillin, phenoxymethyl penicillin, cephalexin, and cephaloglycin (taken 30 minutes before eating) all produce urine concentrations in excess of 100 μg per ml

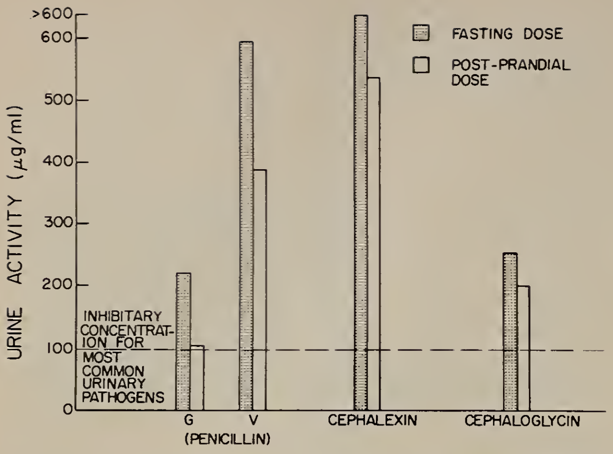

Chart 2.—Urine activity of 2 penicillins and 2 cephalosporins after standard 500 mg per oral doses compared to the minimal inhibitory concentration required to inhibit most strains of *E. coli* and *Proteus mirabilis* recovered from urine (dashed line).

in patients with normal renal function except when there is very heavy diuresis with dilution of the drug in the urine. In a large series of patients,[4] cure was obtained with these urinary levels (except in the presence of obstruction or stone), as expected. It follows, that when a patient is treated for bacteriuria for several days with penicillin or cephalosporin, cure can be expected. If the bacteriuria disappears and does not recur (as documented by culture of a clean voided mid-stream urine) two to six weeks after completing therapy, that infectious episode has been cured. On the other hand, the persistence of bacteriuria, or its recurrence two weeks after completing a course of one of these agents, should suggest a chronic focus of infection, either as chronic pyelonephritis, obstruction or stone somewhere in the urinary system. Appropriate diagnostic and therapeutic procedures should then be instituted.

In the presence of severe renal dysfunction (unilateral or bilateral) it may be impossible to get a large enough concentration of one of these drugs in the urine to inhibit the urinary tract pathogen. This is especially frustrating in cases of unilateral renal disease with bacteriuria originating in the damaged kidney. In this situation (Chart 3) the normal kidney excretes nearly all of the antibiotic, and very little appears in the urine from the diseased, infected kidney.[5] Here, bacteriuria often persists until a more effective agent is used.

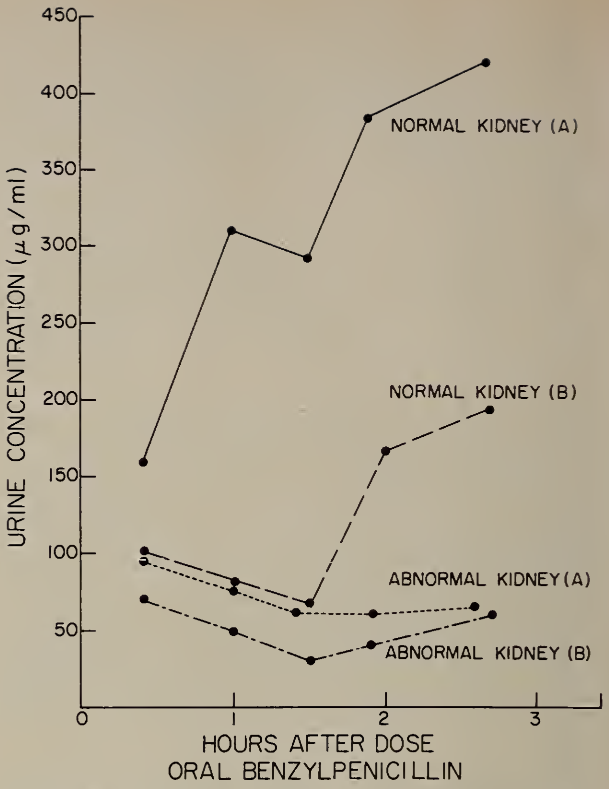

Chart 3.—Comparison of urine concentrations of benzylpenicillin from normal and diseased kidneys in patients with unilateral pyelonephritis. Benzylpenicillin was preferentially excreted by the normal kidney in both cases and adequate (100 μg/ml) amounts of benzylpenicillin did not appear in the urine from the infected kidney.

Parenteral Antimicrobials

Successful parenteral therapy of most nontuberculous bacterial infections can be accomplished with benzylpenicillin, ampicillin, nafcillin, cephalothin, cephaloridine, kanamycin or gentamicin. In some circumstances, carbenicillin may add to the therapy and, therefore, deserves comment regarding therapy of Pseudomonas infections.

Staphylococcal infections. Parenteral therapy of staphylococcal infections should be with a compound active against lactamase producers (the strains resistant against benzylpenicillin and ampicillin) until the infecting staphylococci have been proved susceptible to benzylpenicillin. If there are any inconsistencies in susceptibility tests performed by the single disc method or if the disc test results shows intermediate or indeterminate susceptibility to penicillin G or ampicillin, further tests must be done before the absence of a lactamase is proven. This time period requires therapy with an effective agent that is not going to be destroyed by the staphylococcal penicillinase.

Experiences with nafcillin, cephalothin and cephaloridine have documented their efficacy. In a very large series nafcillin was found as active against penicillin resistant strains as penicillin G was against penicillin susceptible strains.[6] Similarly, when used in proper doses, cephalothin was effective in 95 percent of S. aureus infections.[7] Since cephaloridine was comparable to cephalothin in curing patients with serious S. aureus infections,[8] it becomes apparent that these three compounds (all of which are active against producers of penicillinase) are to be preferred for the treatment of staphylococcal infections. There have been occasional reports of persistent bacteremia in patients receiving cephaloridine for S. aureus endocarditis, and therefore it seems prudent to use large doses of cephalothin or nafcillin in this situation.

Most therapeutic problems of serious S. aureus infections requiring parenteral therapy raise three questions: First, what is the optimal dosage for S. aureus pneumonia, meningitis, endocarditis or severe bacteremia arising from another source? The answer seems to be that large doses by continuous infusion or at short intervals so as to provide a lethal amount of the drug in the blood at all times. This is best accomplished by planning dosage on a mg per kg basis, delivering an initial loading dose, then infusing at a rate sufficient to maintain lethal blood levels. Intermittent infusions via a volutrol attachment can provide higher peak levels, but unless the duration between doses is sufficiently close, there may be long periods without adequate therapy. The most efficacious way to deliver antibiotics by intermittent doses is to shorten the time between doses so that a given dose is administered before the preceding dose is completely eliminated. When a given mg per kg per day schedule is divided into six or eight infusions (to be given every four hours or every three hours) peak serum levels are not unnecessarily high and the long periods without therapy are avoided. This is shown in Chart 4 for cephalothin. A total of 12 grams per day was desired. When given as 3 grams 6 hourly via volutrol as a 30-minute infusion, peak serum activity was very high, but two hours after the infusion the serum activity had fallen to less than 20 μg per ml. A more efficient use of the 12 gram per day schedule occurred when 1.5 grams were given 3 hourly. Peak serum activity varied from 80 to 100 μg per ml, the serum activity was nearly always more than 20 μg per ml, and the average serum activity throughout the entire day (indicated by the hatched areas in the chart) was twice that accomplished with a 6 hourly dosage schedule. This principle of decreasing the duration between doses will always increase serum activity, especially when the drug has a short half-life in serum.[9] Recommendations for parenteral therapy of S. aureus infections are given in Table 3.

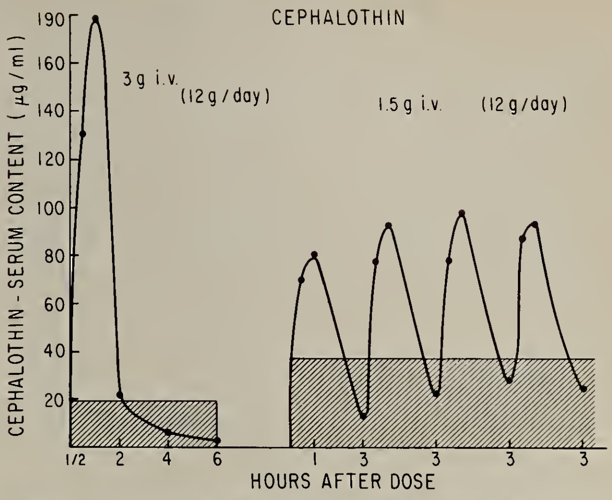

Chart 4.—Comparison of 2 dosage regimens for intravenous cephalothin. Although 6 hourly doses of 3 gm each provide higher peak activity (solid lines), the average serum activity is higher when smaller doses are given at 3 hour intervals (hatched areas).

Two situations that merit special consideration are bacterial meningitis and patients with renal failure. Cephalothin should be avoided in the treatment of meningitis because it does not provide optimal antibacterial activity in the cerebral spinal fluid. On the other hand, cephaloridine provides excellent antibacterial activity in the cerebral spinal fluid and has been valuable in treating pneumococcal meningitis.

In patients with renal dysfunction, drugs that ordinarily would be eliminated by the kidneys accumulate in serum unless the dosage is reduced. Although cephalothin accumulates slowly and is metabolized to desacetylcephalothin, there have been no significant ill effects noticed. Because of this safety factor, cephalothin has gained popularity in patients with shock or renal failure or both. In contrast, cephaloridine does accumulate in the serum if the renal clearance mechanism is

TABLE 3.—*Recommendations for therapy of Staphylococcus aureus infections until organism is proved susceptible to benzylpenicillin.*

Drug	*Route*	*Dosage*	*Frequency of dose*	*Method of administering*
Nafcillin (Unipen)				
A. Life-threatening infection	Intravenous	25 mg/kg BW*	4 hourly	Loading dose of 50 mg/kg BW, then intravenous infusion via volutrol.
B. Moderately severe infection	Intravenous	25 mg/kg BW	6 hourly	Same as in A.
Cephalothin (Keflin)				
A. Life-threatening infection	Intravenous	25 mg/kg BW	3 hourly	Loading dose of 50 mg/kg BW, then via volutrol infusion.
B. Moderately severe infection	Intravenous	25 mg/kg BW	4-6 hourly	Same as in A.
Cephaloridine** (Loridine)				
A. Life-threatening infection	Intravenous	15 mg/kg BW**	6 hourly	Load with 15 mg/kg BW, then via volutrol infusion.
B. Moderately severe infection	Intramuscular	15 mg/kg BW**	6 hourly	Intramuscular

*BW=body weight
**Do not exceed 4 grams total daily dose limit. See Table 4 for dosage schedule for patients with renal failure.

TABLE 4.—*Dosage of cephaloridine in patients with renal dysfunction (impaired clearance of creatinine-Ccr).**

Ccr ml/min/ 1.73m^2	*Blood urea nitrogen-mg %*	*Serum creatinine mg %*	*Daily dosage*	*Dosage schedule*	
80	20	1.4	50-60 mg/kg	15 mg/kg	** 6 hrly
60-80	20-24	1.4-1.6	35 mg/kg	12 mg/kg	6 hrly
40-60	25-34	1.7-2.0	25 mg/kg	8 mg/kg	8 hrly
20-40	35-49	2.1-3.5	15 mg/kg	5 mg/kg	8 hrly
5-20	50-75	3.6-7.0	6 mg/kg	2 mg/kg	8 hrly
less than 5	75	7.0	3 mg/kg	1 mg/kg	8 hrly

**Total daily dose not to exceed 4 grams per day.*

***When 2.5 ml diluent is added to 1-gram vial, concentration is 300 mg per ml.*
When 10 ml diluent is added to 1-gram vial, concentration is 100 mg per ml.

significantly damaged and in rabbits and monkeys nephrotoxicity occurs when very high doses are given.[10] Since cephaloridine, like cephalexin, is not metabolized and is dependent on the kidneys for elimination, regulation of the doses in accordance with renal function should obviate any potential hazard to patients. This can be accomplished by following the dosage schedule suggested in Table 4.

Ampicillin and benzylpenicillin for parenteral use. The usual Streptococcus pyogenes or Diplococcus pneumoniae infection responds to intramuscular benzylpenicillin with little effort by the physician. On the other hand, meningitis, endocarditis, and occasional lung or bone infections often require more sophisticated therapy for reasonable results. In patients with alteration in the blood brain barrier, which ordinarily prevents unlimited transfer of penicillins to the cerebral spinal fluid and brain tissue, excessive dosage of penicillin, especially in patients with renal dysfunction, can cause serious, even fatal, neurotoxicity. Therefore, in the very sickest patients where survival with a return to normal is dependent on all systems of therapy working optimally, it is imperative to use sound pharmacologic principles in prescribing antibiotic therapy.

When benzylpenicillin is given by an intravenous bolus (Chart 5) very high peak concentrations occur in the serum. The example shown using 1,200,000 units of penicillin G, provided nearly 500 μg per ml of serum activity. This is impressive to see, but what does this mean in terms of killing Streptococcus pyogenes, Diplococcus pneumoniae or susceptible Staphylococcus aureus? Since these organisms are killed

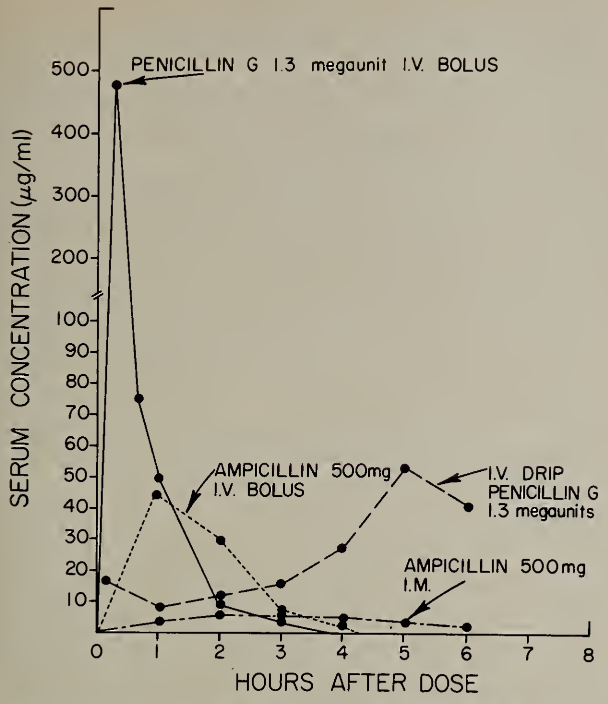

Chart 5.—Comparison of bolus administration of penicillin G and ampicillin to intravenous drip of penicillin G or intramusclar ampicillin (see text).

when exposed to from 0.01 to 0.05 μg per ml of the drug, we have serum activity nearly 10,000 times the amount required for killing. Furthermore, following the peak level there is very rapid elimination of the penicillin via the kidneys (valuable drug down the tube—so to speak) so that within 4 hours penicillin activity has disappeared from the serum. Since intravenous drip therapy, although somewhat erratic in providing uniform blood levels, does provide 200 to 1000 times as much penicillin as is necessary to kill the pathogens (dashed line in Chart 5), this seems a more rational mode of administration. Since the cases of neurotoxicity caused by benzylpenicillin have occurred when excessive serum levels were present, it seems prudent to avoid excessive levels.

Ampicillin, which has become popular as a broad-spectrum drug for therapy of infections caused by Hemophilus spp., Salmonella spp., Proteus spp. and Escherichia coli, is active in killing the susceptible strains in amounts ranging from 0.01 to 5 μg per ml for the Hemophilus, and from 1 to 10 μg per ml for the other pathogens mentioned. It is evident that although intramuscular ampicillin in the usual 500 mg dose (Chart 5) provides marginal or inadequate serum concentrations for killing these pathogens, the intravenous bolus delivery of 500 mg of ampicillin does provide serum activity about 10 μg per ml for about 3 hours. Therefore, 3 hourly bolus delivery or continuous infusion of ampicillin is preferred.

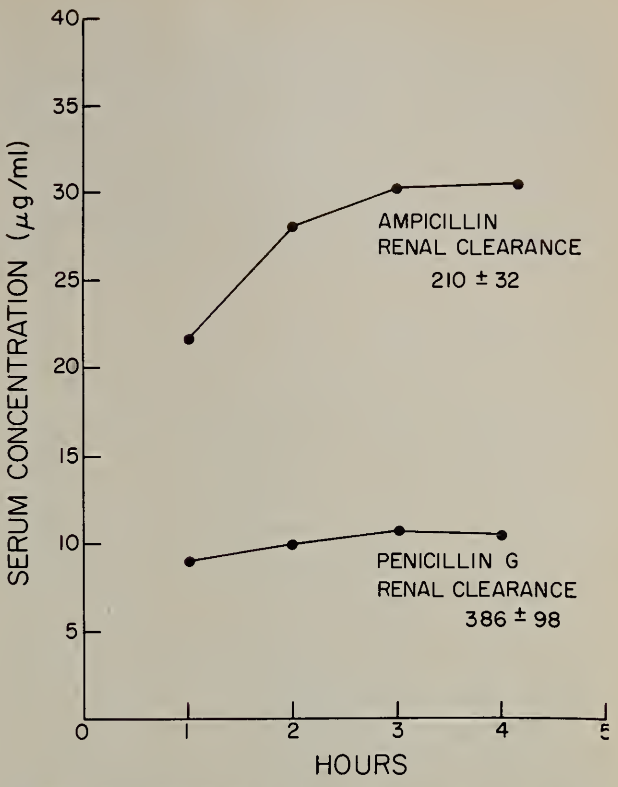

Chart 6.—Comparison of blood levels for ampicillin and penicillin G when the infusion rate is 0.5 gm per hour. Less renal clearance of ampicillin allows higher serum levels.

In certain cases requiring prolonged therapy with high serum concentrations of antibiotic, this may be better achieved with ampicillin than with penicillin G (Chart 6). It is of interest that serum levels of ampicillin can be achieved that are thrice those of benzylpenicillin when similar doses (0.5 grams per hour, which is equivalent to 19,200,000 units per day) are infused. This is because of the slower renal clearance of ampicillin.[11] Additionally, the presence of renal failure would mean more rapid accumulation of ampicillin, as has been documented in patients recovering from surgery requiring cardiopulmonary bypass.[12] Thus, a decrease in doses is required in patients with poor renal elimination mechanisms. It is evident that repeated 6 or 8 hourly doses would quickly lead to excessive blood levels, and since these high levels are unnecessary and are potentially toxic, a reduction in dosage is indicated. Furthermore, hemodialysis and peritoneal dialysis have little effect on the removal of these drugs from the serum. Therefore, the best guide seems to be reduce the dose to reasonable amounts, give it 12 hourly and measure the serum activity of the penicillin G or ampicillin in patients with significant renal failure.

Aminoglycosides

Until gentamicin was available, the favorite "panaceamycin" was a combination of cephalothin and kanamycin. The obsolescense of this combination and the proliferation of various combinations of drugs with gentamicin suggest the futility of shotgun combinations of antimicrobials. Synergism does exist but is uncommon. To date the only useful synergistic action of either of these drugs seems limited to that seen against enterococcal isolates in combination with benzylpenicillin, phenoxymethyl penicillin, or ampicillin.[13] Frequently, a particular pseudomonas species can be shown susceptible to the synergism of carbenicillin and gentamicin.[14] In these circumstances combined therapy guided by appropriate laboratory documentation of synergism seems appropriate. In other circumstances shotgun combinations usually cannot be justified. Selection and dosage regulation of these drugs requires knowledge of two facts. First, the pattern and frequency of kanamycin resistance of the Enterobacteriaceae isolated in the hospital where the patient is located should be known, and second, dosage of the drugs should be high enough and they should be given often enough to provide frequent or constant lethal serum concentrations, yet avoid toxicity.

Kanamycin. A vast experience over many years has made it quite evident that most aerobic Gram-negative bacilli causing human infection can be effectively eradicated by adequate doses of kanamycin if the strain is susceptible. Emergence of kanamycin resistance in certain areas of the world has caused concern, and rightly so. However, it remains a fact that a large majority of strains recovered from all but a few troubled hospitals do not possess resistance to kanamycin and, therefore, can be effectively treated with this agent. If a given hospital has a high frequency of kanamycin-resistant isolates of Gram-negative bacilli, this should be known to the physicians using this hospital and should cause two actions. First, choose another drug while awaiting reports of susceptibility, and, second, seek epidemiologic assistance in identifying the source and spread of the kanamycin resistant strains.

In the absence of significant kanamycin resistance in a given hospital, strains of Klebsiella pneumoniae, Enterobacter aerogenes (formerly Aerobacter), E. coli and less commonly recovered Proteus spp, Serratia marcescens, and others that may possess resistance to ampicillin or the cephalosporins are usually susceptible to kanamycin. If susceptibility is confirmed by an appropriate test, successful therapy can be expected.

One hindrance to effective therapy with kanamycin has been improper dosage because of the fear of toxicity by some physicians or unawareness of this toxic potential by others. Toxicity can usually be avoided by attention to the fact that elimination of kanamycin is impaired in premature infants, neonates, the elderly, in patients with known renal disease, and in patients with transient renal failure due to poor perfusion of the kidney as seen in shock.[15] In these patients, it is essential to prescribe doses on a mg to kg basis and make appropriate adjustments for the impaired elimination. Recommendation for kanamycin doses are summarized in Table 5.

Gentamicin. This aminoglycoside antimicrobic has the most *in vitro* activity of the available compounds against most isolates of Pseudomonas aeruginosa. Additionally, it has excellent activity against many of the other Gram-negative bacilli such as E. coli, Klebsiella spp, Enterobacter aerogenes, and Proteus spp. For these reasons, it has become a popular agent for the treatment of many serious infections, yet has not been a "panaceamycin." Early experiences with gentamicin detected its potential for ototoxicity and nephrotoxicity. Cautious optimism about its efficacy was clouded as the doses were reduced to one or two mg per kg per day and further reductions were made in patients with renal failure. These "adjustments" led to regimens that often failed to provide serum levels sufficient to inhibit the pathogen, and often the infection progressed.

A plan for rational therapy with gentamicin requires recognition that there is a narrow range between therapeutic and toxic levels. The serum levels attained by most other antimicrobics are usually much higher than the minimal inhibitory

TABLE 5.—*Doses of Kanamycin adjusted for variations in renal handling of Kanamycin.*

Patient description	*Half-life in serum (hours)*	*Size and frequency of dose*	*Expected serum concentration (μg/ml)*	*Expected urine concentration (μg/ml)*
Infants (<3 weeks of age)	6-9	5 mg/kg/12 hr	12-15	50-300
Premature infants	6-9	5 mg/kg/12 hr	12-18	100-600
Children >3 weeks of age (not premature)	5.1	7 mg/kg/12 hr	12-15	100-800
Adults				
Serum Creatinine Value				
1	5.1	7 mg/kg/12 hr	10-30	100-300
2	7.6	7 mg/kg/20 hr	10-30	50-100
3	10.1	7 mg/kg/30 hr	10-30	<50
4	12.6	7 mg/kg/36 hr	10-30	<50
5	15.1	7 mg/kg/45 hr	10-30	<50
6	17.6	7 mg/kg/52 hr	10-30	<50
7	20.1	7 mg/kg/60 hr	10-30	<50
8	22.6	7 mg/kg/70 hr	10-30	<50
9	25.1	7 mg/kg/75 hr	10-30	<50
10	27.6	7 mg/kg/84 hr	10-30	<50

concentration (MIC) for the pathogen; but this is not true for gentamicin, where the serum level, toxic concentration, an amount necessary to exceed the MIC for sensitive bacteria all range between 2 and 12 μg per ml. To overcome the hazards posed by this relationship, it is necessary to schedule drug administration so as to provide high enough serum concentrations for killing of the bacteria, yet to avoid exceeding 12 μg per ml in the serum and, therefore, avoid toxicity. Common sense would suggest that smaller, more frequent doses would distribute the drug more efficiently than large infrequent doses. A sophistocated pharmacologic model has confirmed this.[16] It has been shown that in patients with normal elimination of drug via the renal clearance mechanism, administration of 1.7 mg per kg at 8-hour intervals provides serum concentrations that peak between 5 and 8 μg per ml and are usually in excess of 1 μg per ml throughout the entire therapeutic period between doses. In an occasional patient, there is more rapid clearance and, therefore, some period of time without significant activity, but these patients are apparently uncommon.[17] When the dosage is reduced to 1 mg per kg given 12 hourly, peak serum activity rarely exceeds 5 to 6 μg per ml and there is a matter of hours before the next dose when there is no significant gentamicin activity in the serum. This may explain some failures of therapy that have occurred with this drug. This dose reduction was further emphasized in patients with renal failure and the time between doses was extended. This prevented toxicity and accumulation of gentamicin in many patients, but it also allowed long periods of non-inhibitory activity to exist in the patient's serum. To overcome this problem, studies of gentamicin half-life, which is determined by the clearance of creatinine (CCR) for a given patient, were related to an elimination constant K_2 where,

$$K_2 = \frac{\log_{n2}{}^{16}}{T\frac{1}{2}.}$$

It was found that the elimination constant (K_2) was linearly proportional to the CCR value when the CCR was less than 70 ml per min per 1.73 square meter of body surface. Thus, in patients with CCR values in excess of 70 ml per min, gentamicin elimination is normal and the dose should be 1.7 mg per kg 8 hourly. However, patients with CCR values less than 70 ml per min per 1.73

TABLE 6.—*Dosage of gentamicin for patients with abnormal renal function (impaired clearance of creatinine).*

Clearance of creatinine ($ml/min/1.73m^2$)	*Gentamicin dose in mgm/kg every 8 hours*
70 or greater	1.7
60	1.5
50	1.3
40	1.0
30	0.8
20	0.6
10	0.33
8	0.25
4	0.20
2 or less	0.13

square meter have a prolonged serum T ½ of gentamicin and unless the dose is reduced, accumulation and toxicity occur. Since elimination is dependent on ccr, it was possible to develop a dosage nomogram to allow selection of the maintenance dose to provide near steady state serum gentamicin activity. This maintenance dose was derived by the formula,

$$\text{maintenance dose} = \frac{\text{normal dose} \times K_2}{K_2 \text{ at normal elimination.}}$$

These dosage recommendations are provided in Table 6. The efficacy of this regimen has been documented in the therapy of numerous seriously infected patients where serum gentamicin was measured several times daily and proved to be in the therapeutic range, yet avoided the toxic range.[16]

Additionally, in patients with renal failure requiring dialysis, the habit of giving loading doses at the end of one dialysis and waiting until the beginning or end of the next dialysis for another dose often led to peak serum concentrations in excess of 12 μg per ml after the loading dose and then long periods without serum gentamicin activity preceding the next dialysis. This can be overcome by administering a loading dose of 1 mg per kg after each dialysis and again giving small doses 8 hourly, regulated by the creatinine clearance as shown in Table 6, until the next dialysis.[16] This will provide therapeutic yet nontoxic serum concentrations in these patients.

Carbenicillin. Pseudomonas aeruginosa infections have been a problem in patients receiving immunosuppressive therapy for malignant disease or transplantation, in patients who have multiple injuries and require tracheostomy and numerous indwelling tubes and catheters, as well as in burn patients. Carbenicillin, when given in doses that range from 16 to 30 grams per day, has activity against many strains of pseudomonas isolated from these patients. Gentamicin has the greatest activity of any of the known antimicrobials against most species of pseudomonas. Since pseudomonas possess the capability for the rapid transition to resistance to carbenicillin, it has been necessary to supplement carbenicillin therapy with another compound like gentamicin. Although many strains of pseudomonas can be shown to be subject to the synergistic combination of carbenicillin and gentamicin, that is not uniform. On the other hand, nearly all strains are susceptible to gentamicin alone and when used in therapeutic doses it seems to be efficacious. Although there has been enthusiasm for the combination of carbenicillin and gentamicin in the treatment of febrile episodes in the types of patients described above, hazards of gentamicin toxicity are further complicated by the hazards of the combined drug toxicity. Until further experience is gained, it would seem wise to limit the use of carbenicillin to the treatment of patients where there is a proven synergistic activity between carbenicillin and gentamicin or another compound.

Summary

Most patients who require oral antimicrobial therapy can be treated with benzylpenicillin or phenoxymethylpenicillin. In staphylococcal infections, the necessity to prove the absence of ability to produce a Beta lactamase (penicillinase) requires that therapy be with an antistaphylococcal agent effective against penicillinase producers until susceptibility to benzylpenicillin is proven. This is best accomplished by giving a compound such as cloxacillin or cephalexin, both of which are resistant to the hydrolysis and destruction by the lactamases. In infections requiring parenteral therapy the same can be said of nafcillin or cephalothin. In the case of Gram-negative bacillary infections, most of the common isolates for most patients will be susceptible to a cephalosporin and in the more severe infections where cephalosporin resistance is apt to be a problem, kanamycin has proven its worth through many years of use. In certain circumstances hospitals will become inhabited with kanamycin resistant strains of Gram-negative bacilli and in these circumstances gentamicin is usually effective.

As older patients and patients with deteriorating renal function from a multitude of causes become more a part of our patient population, it is necessary to make dosage adjustments to avoid iatrogenic complications from the antimicrobial therapy. In order to do this intelligently, dosage schedules based on elimination of the drug at various levels of renal function have been developed for certain compounds such as cephalexin, cephaloridine, kanamycin and gentamicin, and these recommendations are included. In certain circumstances synergism due to combination of antibiotics seems well proven. The most clearly documented in situations other than tuberculosis are with enterococcal infections where combinations of penicillins and aminocyclitols are often synergistic, and in pseudomonas infections where a combination of carbenicillin and gentamicin may be synergistic. Therapy designed for synergy should be guided by the demonstration of this synergism *in vitro.* Detailed discussions of gentamicin are available in the Second International Symposium on Gentamicin,[18] on the cephalosporins in Proceedings of an International Symposium on Cephalosporin Antibiotics,[19] and on penicillins, cephalosporins, kanamycin in the useful book, Antimicrobial Therapy.[20]

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I think probably the biggest item of misunderstanding among medical people at the present time has to do with the potency of the narcotics currently in use. The majority of people on heroin are taking a very, very weak drug which does not pose the problems of withdrawal that we have had in the past. The vast majority of people can be withdrawn, even from a $50-a-day habit (provided the heroin was obtained from the usual sources in this country), by simple sedation. It's not necessary for all people to go into methadone treatment, narcotic substitution, gradual withdrawal, and so on. This opens up many additional avenues of approach to treatment and certainly shortens therapy a great deal.

—Allan K. Done, M.D., Salt Lake City

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Specialty Conference

Dysautonomia—Its Significance in Neurologic Disease

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Dr. Dreyfus:* Despite the fact that considerable knowledge has been accumulated concerning the anatomy, the physiology and the biochemistry of the autonomic nervous system, dysfunction of this part of the nervous system continues to present diagnostic problems, and dysautonomia is commonly overlooked. It is the purpose of this conference to present the case of a patient who suffered from primary involvement of the autonomic nervous system as well as to review briefly the neurological disorders in which dysautonomia may be an important feature and the various clinical tests which can be employed to demonstrate the dysfunction of this system.

Dr. Vijayan will now present a case which will serve as focal point for the ensuing discussion.

Case Presentation

Dr. Vijayan:† Two years ago a 47-year-old Caucasian woman was admitted to the Sacramento Medical Center for evaluation of postural syncope. Her symptoms, which had begun approximately two years before her admission, included episodes of explosive diarrhea, especially at night, which alternated with brief periods of constipation. At about the same time, the patient began to experience episodes of postural dizziness which increased in severity to such an extent that she fell and injured herself. She complained of excessive dryness of eyes and mouth, the latter requiring the frequent use of mouthwashes. She experienced stress incontinence and urinary urgency. Symptoms of cardiac decompensation developed. The patient denied any significant previous illness.

When examined, signs of congestive heart failure were noted: pronounced anasarca, jugular vein distension and a palpable, tender liver. The heart was moderately enlarged. There was no evidence of valvular heart disease. Pronounced orthostatic hypotension was noted, blood pressure being 120/74 mm of mercury in the recumbent position, 98/58 mm sitting and 84/48 mm standing. The pulse rate remained the same in all three positions. The patient complained of lightheadedness upon assuming the erect position and on occasion syncope developed.

Neurological examination revealed normal men-

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tation. Both pupils measured 4 mm. The pupils did not react to light either directly or consensually; they did react to accommodation. Ciliospinal responses were absent. Fundi were normal. The remainder of the cranial nerves were intact. Motor, sensory and cerebellar functions were normal. Deep tendon reflexes were active and symmetrical bilaterally. No pathologic reflexes could be elicited.

Blood cell count and urinalysis, including tests for Bence-Jones proteins, were within normal limits, as were serum proteins, cholesterol, electrolytes, uric acid, creatinine, bilirubin and blood urea nitrogen. CPK was 40 units, LDH was 175 units and SGOT was 40 units. LDH isoenzyme estimations showed mild elevation of the cardiac fraction. Glucose tolerance test, thyroid function tests, serum immunoelectrophoresis, lipoprotein electrophoresis, 17 ketosteroid and 17 oxysteroid excretion rates, serum cortisol levels, 24-hour catecholamine and VMA excretion tests were all within normal limits. Repeated blood cultures were negative.

Skull films were normal. The cerebrospinal fluid was clear and colorless, was under normal pressure, contained no cells and had a protein content of 102 mg per 100 ml. Spinal fluid sugar was 75 mg per 100 ml and concomitant blood sugar was 170 mg per 100 ml. Measurements of motor nerve conduction velocities and electromyograms of both the upper and the lower extremities were normal.

X-ray films of the chest revealed left ventricular and atrial enlargement. Electrocardiographic tracings showed left axis deviation with a QRS complex of 0.1 second and poor R-wave progression suggestive of an anterior myocardial infarction or severe cardiomyopathy. The patient is reported to have had a normal electrocardiogram before the onset of illness.

Adrenalin and cocaine tests revealed evidence of pupillary sympathetic denervation while the mecholyl test indicated parasympathetic denervation. Tear secretion, as estimated by the Schirmer test, was diminished. Amplitude of accommodation was found to be normal for the patient's age. Elevation of body temperature by 1.5°F produced normal sweating over the trunk but none over all four extremities and the face. Intradermal injection of histamine failed to produce a flare response but a well-formed wheal was observed. Cardiac catheterization demonstrated elevated atrial pressure as well as right and left ventricular end-diastolic pressure. Angiographic visualization of the left ventricular wall revealed it to be thickened. Tilt-table testing and Valsalva maneuver revealed evidence of sympathetic denervation. The patient responded very poorly to induced hypoxemia, demonstrating no change in ventillatory rate. Further details of the patient's abnormal respiratory responses have been the subject of an earlier report.[1]

A rectal biopsy, performed because of the combination of cardiomyopathy and autonomic neuropathy, revealed deposits with the staining properties of amyloid surrounding peripheral arterioles. Therefore, a diagnosis of amyloidosis was seriously entertained.

The patient received symptomatic treatment with frequent follow-up visits. She made a gradual but definite recovery and seven months later no longer complained of postural dizziness, although her blood pressure readings remained abnormal—110/70 mm of mercury in both the supine and erect positions. Reflex increase in pulse rate was absent. Cardiac size decreased considerably and was normal 14 months after the onset of the illness. Dryness of mouth and eyes disappeared, but gastrointestinal symptoms tended to persist. The patient did not show any further neurological progression. A gum biopsy obtained 14 months after discharge showed no evidence of amyloid deposits.

Although a diagnosis of amyloidosis appeared to have been established, the gradual improvement and lack of progression cast serious doubt upon this diagnosis. The clinical course of the illness is more in keeping with a primary autonomic neuropathy of autoimmune type. However, the cause of the cardiomyopathy remains unexplained.

Dr. Dreyfus: Thank you, Dr. Vijayan. Dr. Wichser will now discuss the neurologic diseases which are associated with dysautonomia.

Disease States Associated with Neurogenic Dysautonomia

*Dr. Wichser:** Table 1 summarizes the various disease states in which either the peripheral or the central autonomic nervous system is involved either in a diffuse or a partial manner.

Autonomic dysfunction may constitute a prominent clinical feature of a number of peripheral

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TABLE 1.—*Disease States Associated with Neurogenic Dysautonomia*

1. *Disorders of the peripheral autonomic nervous system*
    - A. *Diffuse Involvement*
        - Peripheral polyneuropathies: diabetes, amyloidosis, Guillain-Barré syndrome, porphyria, B_{12} deficiency, alcoholism
        - Tabes dorsalis
        - Drugs and toxins interfering at a peripheral level
        - Familial dysautonomia (Riley-Day syndrome)
    - B. *Partial Involvement*
        - Horner's syndrome
        - Raeder's syndrome
        - Adie's tonic pupil
        - Carotid sinus syndrome
        - Hirschsprung's disease
2. *Dysautonomia of central origin*
    - A. *Degeneration or Focal Lesions Involving Central Autonomic Structures*
        - Idiopathic orthostatic hypotension (Shy-Drager syndrome)
        - Idiopathic Parkinson's disease
        - Vascular accidents
        - Neoplastic infiltration
        - Demyelination
        - Infection
        - Trauma
    - B. *Developmental Abnormalities*
        - Syringomyelia
    - C. *Drugs and Toxins Acting at a Central Level*

nerve disorders of toxic or metabolic cause. Since motor and sensory symptoms and signs are usually more conspicuous and readily recognized, dysautonomia tends to be overlooked. Autonomic dysfunction, however, may constitute the leading and most striking neurologic symptoms in patients afflicted with diabetes, amyloidosis and the Guillain-Barré syndrome.

Involvement of the autonomic nervous system is particularly prominent in diabetic polyneuropathy in which sympathetic denervation of the cardiovascular system causes orthostatic hypotension without compensatory tachycardia. The patient may complain of symptoms suggestive of disturbed gastrointestinal motility. Symptoms such as dysphagia, vomiting of undigested food indicative of delayed gastric emptying time, intermittent nocturnal or postprandial diarrhea and, on occasion, fecal incontinence are quite common. Sexual impotence caused by erectile incompetence and disturbances of micturition such as hesitancy and urinary retention may be the earliest symptoms of diabetic involvement of the peripheral nervous system. On occasion the patient displays an unusual disorder of perspiration consisting of excessive sweating over the upper half of the body, primarily in the face, neck and axillae, accompanied by anhydrosis below the waist along with a subjective feeling of heat intolerance. A miotic pupil which responds slowly and incompletely to light is indicative of autonomic disturbance of pupillomotor function.[2]

The autonomic nervous system is quite commonly affected in patients with generalized amyloidosis, even in the absence of striking motor and sensory neuropathy.[3,4]

Autonomic dysfunction of some degree is usually present in instances of polyneuropathy of autoimmune etiology (Guillain-Barré syndrome), but symptoms are usually largely overshadowed by the more prominent motor and sensory manifestations. The literature contains one report of acquired pure pan-dysautonomia of gradual onset over a period of months, followed by gradual, and eventually complete, recovery. In this case, the somatic nervous system remained unscathed. During the peak of the illness, the cerebrospinal fluid protein content was elevated. It has been tentatively concluded that acquired peripheral dysautonomia of this type has an autoimmune etiologic basis similar to that of classical polyneuropathy of the Guillain-Barré type.[5]

Autonomic dysfunction may also accompany the polyneuropathy engendered by chronic alcoholism.[6]

Drugs which act as ganglionic blocking agents and toxins, such as that elaborated by the botulinum organism, which inhibit the release of acetylcholine at the motor endplate and cholinergic autonomic synapses can be held responsible for symptoms of dysautonomia.

Since Riley and Day first reviewed the topic of familial dysautonomia,[7] a number of publications dealing with the mode of inheritance and the clinical, physiologic and pathologic features have appeared in the literature. The disease appears to affect children of eastern European Ashkenazy Jewish ancestry exclusively. It appears doubtful that cases reported among non-Ashkenazy Jewish children are in fact instances of familial dysautonomia of the Riley-Day type.[8] If the strict criteria required for the diagnosis of Riley-Day syndrome are met, it is likely that in these cases it has not been possible to trace the patients' ancestry with complete accuracy. The Riley-Day syndrome follows an autosomal recessive mode of inheritance. Males and females are equally afflicted. In the North American Jewish population, the frequency of the disorder has been estimated at one in ten thousand to twenty thousand live births.[9] In Israel the calculated gene frequency amongst Ashkenazy Jews is 1 percent, while not a single incidence of the disease has been reported among Jews of Sephardic stock, who account for 50 percent of Israel's population.[10]

The clinical manifestations of the Riley-Day syndrome[11,8] encompases more than autonomic dysfunction. Sensory disturbances are conspicuous, with decreased pain and temperature sensations, leading to mutilation secondary to injury. Charcot's arthropathies are not uncommon. Vibratory and position sense is always intact. The absence of sense of taste accompanied by the absence of fungiform papillae of the tongue are pathognomonic features of the disease. (In asymptomatic members of an afflicted family, fungiform papillae are either normal in number, diminished or absent.) Circumvallate papillae may be diminished or absent. Motor function tends to be normal. Clumsiness of movement and dysarthric, slurred, monotonous and nasal speech are common. Deep tendon reflexes are either hypoactive or absent. Mentation is frequently retarded and the child tends to be emotionally labile—perhaps a result of environmental factors engendered by the disease. Kyphoscoliosis is not uncommon and is believed to be of neurogenic origin. Episodic bouts of fever of unknown and obscure cause have been described.

Children afflicted with the Riley-Day syndrome demonstrate defective lacrimation with an absence of overflow tearing. This, together with corneal hypesthesia, may result in ulcerations of the cornea. On occasion anisocoria and sluggish pupillary reaction may be present.

Gastrointestinal symptoms manifest themselves very early in life. A history of difficulty with feeding, characterized by dysphagia, spitting, drooling, choking and aspiration, is almost invariably elicited. Aspiration frequently leads to bouts of bronchopneumonia. As the child grows older, dysphagia becomes less prominent but intermittent diarrhea, constipation, sphincter incompetence and cyclic vomiting become the most noted symptoms.

Respiratory symptoms other than bronchopneumonia consist of prolonged breath-holding spells indicative of a failure to respond appropriately to hypoxic and hypercapnic stimuli.

Cardiovascular symptoms characterized by orthostatic hypotension without concomitant tachycardia are common. Stress may induce paroxysmal bouts of hypertension and tachycardia, blotching of the skin and akrocynosis. These symptoms may lead one to a mistaken diagnosis of pheochromocytoma.

Dysfunction of exocrine glands, as evidenced by deficient lacrimation and excessive sweating in response to excitement or stress, can be demonstrated.

The prognosis in the majority of cases of Riley-Day syndrome is poor and only a small number of children reach adolescence or early adulthood.

The pathology of familial dysautonomia has been the subject of fragmentary reports and no consistent abnormalities have been described as yet. A recent electron microscopic study of somatic peripheral nerves has shown a pronounced reduction in the number of unmyelinated fibers and a scarcity of large myelinated fibers measuring more than 12 microns in diameter. These findings suggest a selective arrest in the development of both unmyelinated and large myelinated fibers, which are genetically derived from one distinct neuronal population. These findings correlate with some of the clinical features of the Riley-Day syndrome. Since large myelinated fibers convey afferent impulses from muscle spindles, their scarcity in familial dysautonomia would account for the typically hypoactive or absent deep tendon reflexes. Unmyelinated C-fibers in somatic peripheral nerves mediate sensations of pain, temperature and taste as well as the axonal reflex observed in response to histamine. All of these functions are defective in the Riley-Day syndrome. A similar abnormality affecting unmyelinated autonomic fibers could readily explain all of the symptoms of sympathetic and parasympathetic denervation. As yet a reduction of unmyelinated autonomic fibers in the peripheral nerves of afflicted patients has not been demonstrated.[12]

An abnormality of catecholamine metabolism has been shown in patients suffering from familial dysautonomia. The urinary excretion of vanillymandelic acid (VMA), a metabolite of norepinephrine, is decreased while urinary homovanillic acid (HVA), a metabolite of dopamine, is increased. These findings indicate a functional block in the conversion of dopamine to norepinephrine. While the enzyme, dopamine-β-hydroxylase (DBH), which catalyzes this conversion, is localized in vesicular structures of sympathetic nerves, enzymatic activity has also been found in human plasma. Recent studies have demonstrated that 25 percent of patients with dysautonomia have no detectable plasma DBH activity and that the mothers of these patients have decreased DBH activity. Since the enzyme and the catecholamine are both released into the plasma, it is conceivable that the plasma levels do not actually reflect tissue levels of the enzyme. A decreased rate of activation within the tissue or defective release of the enzyme could result in low plasma levels.[13,14,15]

Cases of congenital familial sensory neuropathy associated with anhydrosis and other dysautonomic symptoms in many ways resemble the Riley-Day syndrome. However, the disease is not restricted to Ashkenazy Jews and, despite the fact that lingual fungiform papillae and taste buds are present, the sense of taste is absent in these patients.[16]

In 1960 Shy and Drager[17] first suggested that idiopathic orthostatic hypotension was caused by a primary degenerative disorder of the central nervous system.

Even though postural hypotension is the cardinal feature of the disorder, other symptoms of autonomic disturbances, such as atonic bladder, urinary incontinence, disturbed bowel motility, loss of rectal sphincter tone, fecal incontinence, impotence and defective thermoregulatory mechanisms, are usually present.[18]

The dysautonomic symptoms of the Shy-Drager syndrome form only one aspect of a more diffuse neurologic disease. Thus, the full clinical picture encompasses in addition features referable to corticobulbar and corticospinal, lower motor neuron, extrapyramidal and cerebellar dysfunction. Dysautonomia may antedate these symptoms by as many as ten years or it may occur simultaneously. In general, the neurological symptoms assume a wide spectrum.[19]

The course of the disease is one of slow progression over many years. The postural drop of blood pressure with its resultant syncope constitutes the most disabling symptom.

Clinical studies of patients with orthostatic hypotension suggest that the dysautonomic symptoms are caused by a central rather than a peripheral lesion.[20]

The pathological changes demonstrated in cases of Shy-Drager syndrome can be correlated with the clinical picture. Demyelination of pyramidal tracts, loss of neurons in the oculomotor nuclei, anterior horn cells of the spinal cord, basal ganglia, pigmented nuclei of the brain stem and a compensatory gliosis have been demonstrated. In many cases degeneration of the olivo-ponto-cerebellar system is present. Dysautonomia is caused by massive loss of neurons in the dorsal motor nuclei of the vagus, the intermediolateral columns of the spinal cord and the sympathetic ganglia.[21]

Autonomic disturbances have been described in conjunction with Parkinson's disease. In this neurological disorder a wide spectrum of dysautonomic features observed clinically has been alluded to. Very few of these symptoms have been documented by detailed physiological investigations. An exception is the defective baroregulator reflex function which has been described in patients with Parkinson's disease; the faulty temperature regulation occurs as a result of deficient cutaneous reflex vasodilatation and anhydrosis over the body.[22]

In this disease pathologic changes are not confined to the basal ganglia. Neuronal loss in diencephalic autonomic structures, intermediolateral columns of the spinal cord and sympathetic ganglia have also been documented. Clinically and pathologically it appears evident that idiopathic Parkinson's disease and the Shy-Drager syndrome have common attributes.[23]

Only brief consideration will be given to a number of disease entities which affect the autonomic nervous system only in part. Sympathetic denervation of the pupils as part of Horner's syndrome can arise from lesions which involve the first (central), the second (preganglionic) or the third (postganglionic) neuron. When the disease involves the first neuron, the lesion is situated in either the brain stem or the cervical spinal cord. In such instances the Horner's syndrome is only part of a more widespread autonomic dysfunction. Lesions involving the second neuron originating in the cilio-spinal center at the C7-C8-T1 level give rise to a classical Horner's syndrome which includes miosis, ptosis and hemifacial anhydrosis of the homolateral side. The third neuron fibers originate in the superior cervical ganglion. The fibers divide into two branches at the level of the bifurcation of the carotid artery. One branch carries sudomotor and vasomotor fibers, forming a plexus around the external carotid artery, while the other carries oculosympathetic fibers which follow the internal carotid artery into the cranium, subsequently coursing through the superior orbital fissure into the orbit. Thus, lesions of the third neuron will produce complete Horner's syndrome only if they are situated below the bifurcation of the carotid artery.

Lesions which occur along the internal carotid artery, within the cranium or in the orbit result in a partial Horner's syndrome consisting of miosis and ptosis without hemifacial anhydrosis.[24] Raeder's syndrome is a prime example of such a lesion. This is a benign, self-limiting disorder of unknown cause which presents with severe, continuous, unilateral retro-orbital pain accompanied by miosis and ptosis. On occasion hypesthesia in the territory of the ophthalmic division of the trigeminal nerve may be elicited. Pain subsides within a period of months but signs of ocular sympathetic denervation tend to persist. As yet the histopathologic features of this disorder have not been described. The primary form of Raeder's paratrigeminal syndrome must be differentiated from that caused by lesions which involve the parasellar region, such as tumors and aneurysms.

Adie's syndrome represents the parasympathetic counterpart to sympathetic denervation of the pupil. In addition to a tonic pupil, the syndrome also includes hypoactive or absent deep tendon reflexes. The tonic pupil is usually enlarged and its reaction to light is slow and delayed; reaction to accommodation tends to be prompt. Pathologic examination of the parasympathetic ciliary ganglia has revealed nonspecific degenerative changes.[25] A recent report of a patient with Adie's pupil, who was subjected to extensive investigation of autonomic function, describes parasympathetic denervation of the heart as well.[26]

Dr. Dreyfus: Thank you, Dr. Wichser. Now that we have reviewed the principal neurogenic dysautonomic disorders, let us turn our attention to the clinical evaluation of autonomic dysfunction.

TABLE 2.—***Clinical Evaluation of Dysautonomic States***

1. *Hemodynamic regulation*
   - A. *Neural Mechanisms: Response of Blood Pressure and Heart Rate to:*
     - Postural changes (tilt table)
     - Carotid sinus massage
     - Valsalva maneuver
     - Cold pressor test
     - Emotional stress
   - B. *Humoral Mechanisms: Determination in Plasma and/or Urine of:*
     - Renin
     - Angiotensin II
     - Aldosterone
     - Catecholamines
2. *Respiratory regulation*
   - A. *Ventilatory Response to:*
     - Induced hypercapnia
     - Induced hypoxemia
3. *Gastrointestinal motility*
   - Barium meal and enema
   - Intraluminal manometry
4. *Disturbance of micturition*
   - Cystometry
5. *Function of exocrine glands*
   - A. *Assessment of Sweating:*
     - Color indicators
     - Electrical skin resistance
   - B. *Assessment of Tearing:*
     - Schirmer test

Clinical Evaluation of Dysautonomic States

Dr. Wichser: Table 2 summarizes the different ways one can investigate various autonomic functions.

Hemodynamic regulation upon assumption of the upright position involves the interplay between neural and humoral mechanisms and is aimed at proper perfusion of vital organs.[27]

A fall in blood pressure stimulates pressure-sensitive stretch receptors in the carotid sinus and the aortic arch. The baroreceptor reflex is integrated at the brain stem level and is mediated through efferent sympathetic pathways. The response consists of a constriction of vessels leading to increased arteriolar resistance and decreased venous capacitance. This prevents pooling of blood and insures normal venous return of blood to the heart and maintenance of adequate cardiac output. Provided this circulatory reflex is functioning normally, assumption of the upright position is accompanied by a slight and transient drop in blood pressure and only minimal tachycardia.

In dysautonomic states where the baroreceptor reflex is defective, profound hypotension without concomitant tachycardia occurs upon changes in posture. This can be elucidated by obtaining blood pressure readings while the patient is brought rapidly to the erect from the recumbent position or by the use of a tilt table. Carotid sinus massage stimulates the carotid baroreceptors and in the majority of normal persons vasodilatation followed by a drop of blood pressure and bradycardia ensues. This maneuver is not entirely reliable since the response occasionally fails in normal persons. The Valsalva maneuver is another way to evaluate the integrity of the baroreceptor reflex. Forced expiration for 10 to 15 seconds against a closed glottis results in increased intra-athoracic pressure and causes a sudden decrease in heart filling pressure and stroke output. Therefore pulse pressure and mean arterial pressure drop, stimulating the baroreceptors. In normal persons this maneuver enhances arteriolar and venous vasoconstriction, as manifested by an increase and overshoot in diastolic pressure within a few seconds following completion of the maneuver. The overshoot in turn triggers reflex bradycardia which represents a baroreceptor-mediated response to a sudden increase in blood pressure. In dysautonomic states, the Valsalva maneuver results in an exaggerated fall in blood pressure. At the end of the forced expiration, blood pressure rises slowly; there is no overshoot or reflex bradycardia.

While those procedures evaluate the integrity of the entire baroreceptor reflex arc, the cold pressor test and the cardiovascular response to emotional stress yield information concerning the functional state of central sympathetic structures and their peripheral efferent pathways. Immersion of a hand in ice water for five minutes or inducing emotional stress by having the patient perform mental arithmetic in noisy and distracting surroundings normally stimulates a slight rise of blood pressure and heart rate. A failure of this response is suggestive of defective central or efferent peripheral sympathetic mechanisms, not to mention stolidity on the part of the patient.[28]

Hemodynamic regulation is also dependent upon a variety of humoral mechanisms. When released, renin, an enzyme synthesized in the kidney, triggers a chain of biochemical reactions which result in the formation of angiotensin II. Along with ACTH, this vasopressor substance plays an important role in the regulation of Aldosterone secretion. Aldosterone, by virtue of its effect on salt retention, maintains blood volume and pressure. The release of renin is not only dependent upon intrarenal mechanisms but is also under the control of the sympathetic nervous system, as is aldosterone secretion. In normotensive persons with a normal salt intake, the change from the supine to the upright position results in an increase in renin activity and aldosterone secretion. In some patients afflicted with dysautonomia this response may be lacking. In others the intrarenal mechanisms may compensate for the absence of sympathetic control of renin and aldosterone secretion.

Plasma and urinary catecholamines also have been reported to be in the low normal range in dysautonomic subjects. In some cases the normal increase found upon postural changes may be absent. The abnormality of catecholamine metabolism which affects children with familial dysautonomia has been mentioned earlier in this report.

The regulation of respiration can be assessed by the evaluation of ventilatory response to induced hypoxemia and hypercapnia, stimulating O_2 dependent peripheral chemorecptors in the carotid bodies and carbon dioxide dependent chemoreceptors in the brain stem respectively. In normal persons a reduction of pO_2 or an increase of pCO_2 induces sustained hyperventilation. In dysautonomic states this response is reduced and only transient hyperventilation ensues.[29,30,1]

Gastrointestinal motility is easily assessed by radiologic examination. In dysautonomic states a barium swallow reveals a number of abnormalities, including atonic dilatation of the esophagus and slowed transit to the stomach, gastric atony and distension, delayed gastric emptying time and a characteristic small bowel pattern consisting of an increase in frequency and amplitude of peristaltic waves with rapid progression of the barium. A barium enema frequently demon-

TABLE 3.—*Topical and Systemic Use of Pharmacologic Agents for Assessing Autonomic Pathways*

1. *Topical application of pharmacological agents*
   - A. *Pupillary Response to:*
     - Adrenaline 1:1000
     - Cocaine 4%
     - Mecholyl 2.5%
   - B. *Axonal Reflex:*
     - Intradermal histamine 1:1000
2. *Systemic application of pharmacological agents*
   - A. *Monitoring of Blood Pressure and Heart Rate in Response to Infusion of:*
     - Mecholyl
     - Norepinephrine
     - Angiotensin II
   - B. *Monitoring of the Heart Rate in Response to IM Injection of:*
     - Atropine
     - Ephedrine
     - Neostigmine

strates colonic distension and a decrease in propulsive activity.[2] Intraluminal manometry has also been used to demonstrate abnormal gastrointestinal motility.

Disturbances of micturition can be demonstrated by cystometry.

The function of exocrine glands can be elucidated by testing both sweating and tearing. Sweating can be investigated by the application of special color indicators to the skin. A mixture of alcoholic solution of castor oil and iodine is evenly painted on parts of the body. After the solution has dried, a fine dust of rice starch powder is applied. Then the patient is made to perspire by artificial means. The areas in which perspiration is intact will become deep blue while the dry areas remain light. Chinizarin-2-6-disulfonate powder can be used in a similar way. A bluish-purple discoloration indicates areas of intact perspiration.

A more accurate assessment of sweating can be made by the use of electrical skin resistance testing.[31]

Tearing can be estimated in a rough manner by the use of the Schirmer test, which consists of the insertion of one end of a 5 mm wide and 25 mm long strip of thin filter paper into the lower conjunctival sac while the other end hangs over the edge of the lower lid. The moisture of the tears wets the strip of filter paper, producing a moisture front. In normal subjects, after five minutes the moistened area extends over a length of approximately 15 mm. Values below 10 mm are suggestive of hypolacrimia.

Dr. Dreyfus: Thank you, Dr. Wichser, for a most elegant discussion. I will now ask Dr. Vijayan to review the use of topical agents in the assessment of specific autonomic functions.

Dr. Vijayan: Table 3 lists both the topical and systemic applications of pharmacological agents for the assessment of integrity of autonomic pathways.

The topical application of pharmacological agents is extremely useful in the evaluation of pupillary denervation.[32] The rationale behind these special tests is so-called "Cannon's law," or the phenomenon of denervation hypersensitivity. It has been demonstrated that a denervated effector becomes hypersensitive to its particular neurotransmitter substance and to related drugs. The phenomenon takes approximately two to three weeks to develop following denervation of the effector organ.

The instillation of epinephrine in a concentration of 1:1000 into the conjunctival sac of the eye has no effect on the diameter of a normally innervated pupil. As the result of sympathetic denervation, the hypersensitive pupil responds by dilating. The test is best carried out by the instillation of three drops three times within an interval of three minutes. The pupillary size is checked after 15, 30 and 45 minutes. As a rule, hypersensitivity to epinephrine is greatest as a result of lesions which affect the postganglionic fibers and is less prominent in lesions affecting the preganglionic fibers. In lesions which involve central sympathetic pathways, the pupil rarely reacts. If denervation is incomplete, denervation hypersensitivity may not be demonstrable.

The topical application of a 4 percent cocaine solution as a test for sympathetic denervation tends to be more reliable. The test should be carried out as described above. Cocaine potentiates the effect of the adrenergic transmitter since it probably prevents the re-uptake of epinephrine into nerve endings. A normal response to cocaine consists of pupillary dilatation. In sympathetic denervation caused by lesions of the post- or preganglionic fibers, no change in pupillary size occurs, since no transmitter substance is available. In instances of central sympathetic denervation, slight mydriasis occurs.

A freshly prepared solution of 2.5 percent mecholyl can be used in a fashion similar to the above to demonstrate parasympathetic denervation. No response will be demonstrated in the normal eye while denervation hypersensitivity causes miosis.

The intracutaneous injection of 0.05 ml of histamine phosphate in a dilution of 1:1000 normally causes a 1 cm wheal after 5 to ten minutes. Immediately surrounding it one observes a narrow red areola and this in turn is surrounded by an erythematous flare which extends 1 to 3 cm from the border of the wheal. A similar triple response is obtained when histamine is released into the tissue as the result of a scratch. The wheal and the deeply colored red areola are caused by direct action of histamine on blood vessels, while the flare depends upon the integrity of the axon reflex mediated along sensory fibers by antidromic transmission. In familial dysautonomia the flare response is invariably absent. It may also be absent in diseases involving peripheral nerves.[33]

Dr. Dreyfus: Thank you, Dr. Vijayan. Finally we should not forget to mention the systemic application of pharmacological agents which can be used for purposes of monitoring autonomic dysfunction of the cardiovascular system.

These include the infusion of mecholyl at a steady rate. In dysautonomic states this will produce a drop in blood pressure without an increase in heart rate at a lower infusion rate than in normal subjects. In cases of familial dysautonomia, mecholyl restores temporarily the sense of taste, deep tendon reflexes and the flare response to histamine. The mechanism by which this phenomenon occurs is unknown.[34]

The infusion of norepinephrine causes a rise in blood pressure which is usually more pronounced in dysautonomic states than with normal subjects for a given infusion rate.[35] In patients with familial dysautonomia, the infusion of norepinephrine also produces erythematous blotching of the skin identical to that occurring spontaneously as a result of emotional stress. Thus, bouts of hypertension and blotching of the skin observed in dysautonomic children are believed to be due to an exaggerated response to endogenous norepinephrine.

The infusion of angiotensin II into patients with idiopathic orthostatic hypotension also causes an exaggerated blood pressure response.[27] The response to mecholyl and norepinephrine has been ascribed to denervation hypersensitivity to neurotransmitter or related substances. Since angiotensin II is not one of these substances, a different mechanism needs to be invoked. Defective baroreceptor function could provide an alternative explanation. Thus, hypertension induced by angiotensin II, mecholyl or norepinephrine would not lead to compensatory peripheral reflex vasodilatation and bradycardia.

The integrity of autonomic innervation of the heart can be evaluated by the intramuscular injection of atropine, ephedrine and neostigmine while the heart rate is monitored.[27] The intramuscular injection of 0.8 mg of atropine causes a parasympathetic block, normally causing an increase in heart rate by virtue of unopposed sympathetic function. No such change occurs in cases of sympathetic denervation of the heart. Similarly, 25 mg of ephedrine administered intramuscularly results in increased heart rate under normal conditions. In sympathetic denervation this response is absent. Conversely, one mg of neostigmine given intramuscularly results in bradycardia as long as the parasympathetic innervation of the heart in intact.

In this conference we have attempted to describe the clinical features of the most important neurological dysautonomic disorders without going into exhaustive detail. We have also discussed clinical tests which are useful in the evaluation of patients suspected of having autonomic dysfunction.

Since a number of neurologic disease entities may actually present with symptoms of dysautonomia, careful clinical observations and appropriate diagnostic tests are essential. Proper management of these disorders consists of symptomatic treatment along with therapy aimed at the underlying disease. Since some of the symptoms of dysautonomia are crippling or life-threatening, prompt recognition and treatment of them is important.

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LUPUS AND CONTRACEPTION

What means of birth control do you recommend for patients with lupus erythematosus?

Several years ago there was a furor about the possibility that the pill was inducing lupus in a limited number of patients. We studied some 30 women in the Family Planning Clinic and found, with Dr. Bernstein, that there was no evidence of lupus in patients taking contraceptive pills for as long as four to five years. There were no serologic abnormalities and no LE cells. However, since there is an increased risk of phlebitis, generalized vasculitis, and sometimes of edema in patients with lupus it really is not advisable for them to use the pill. Some may insist and use the pill and many will get by without any problems. The pill can be used in a limited number of patients who have severe premenstrual flares or in some with endometriosis. We have had a few patients with endometriosis take as much as 40 mg of Enovid® a day for months to control that problem.

As far as IUD's are concerned, patients with lupus are very susceptible to secondary infections. They seem to tolerate IUD's poorly. They have a lot of pain, discharge, infection, and they frequently have to have the IUD's removed. There are some patients who will tolerate it but it is not advisable.

I think the safest procedure is to advise patients with LE to use the diaphragm and jelly.

—Edmund L. DuBois, M.D., Los Angeles

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Refer to: Hemodynamic consequences of an arteriovenous fistula—Medical Staff Conference, University of California, San Francisco. Calif Med 117:38-43, Oct 1972

MEDICAL STAFF CONFERENCE

Hemodynamic Consequences Of an Arteriovenous Fistula

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr. and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

Dr. Smith:* The topic for discussion today is the hemodynamic consequences of an arteriovenous fistula. The patient will be presented and discussed by Dr. Abbott.

Dr. Abbott:† The patient, a 52-year-old man, was admitted to the Northern California Artificial Kidney Center at San Francisco General Hospital on May 1, 1969, for chronic hemodialysis. Two years before admission a nephrotic syndrome developed due to chronic membranous glomerulonephritis, proved by biopsy. In the two months before admission he had become uremic, requiring repeated peritoneal dialysis. He had a seven-year history of angina pectoris, quiescent for six months before admission to hospital.

On admission to the Artificial Kidney Center, a standard Quinton-Scribner Teflon® cannula was inserted into the right calf and a subcutaneous radial artery-cephalic vein arteriovenous fistula was created in the right forearm. Following hemodialysis training, the patient was discharged and performed hemodialysis three times a week at home. However, persistent systolic hypertension required administration of methyldopa, 250 mg twice a day, and one month later he was readmitted because of prolonged angina pectoris. Although myocardial infarction could not be documented, arteriosclerotic heart disease was again diagnosed. Atrial fibrillation developed and required direct-current cardioversion. Maintenance digoxin and quinidine therapy were then begun. In spite of this therapy, congestive heart failure developed. Cardiac catheterization was performed, and hemodynamic measurements were carried out in a control state and with both the shunt and the fistula temporarily occluded (Table 1). The results revealed low normal cardiac output, left and right heart failure, and no significant change in hemodynamic measurements between control and temporary occlusion states. During the stay in hospital pain and coolness in the right hand were first noted when the hand was used or raised above waist level, although it was learned from careful questioning of the patient that ischemic symptoms had been present in the right hand since creation of the fistula. Superficial ulcerations were present on the right thumb and forefinger. Plethysmographic studies revealed decreased blood flow in the right thumb and increased blood flow in the right forearm. Brachial arterial angiography confirmed a radial fistula "steal" complex (Figure 1). Surgical exploration was carried out. Blood flow

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*Lloyd H. Smith, Jr., M.D. Professor and Chairman of the Department of Medicine.

†Joseph A. Abbott, M.D., Assistant Clinical Professor of Medicine and Assistant Director of the Cardiopulmonary Unit, San Francisco General Hospital.

TABLE 1.—*Cardiac Catheterization Results*

Hemodynamic Parameter	*Control State*	*Fistula and Shunt Occlusion*
Heart Rate (beats/minute)	86	82
Blood Flow		
Cardiac Output	4.9 L/min	4.6 L/min
Cardiac Index	2.6 L/min/M^2	2.5 L/min/M^2
Blood Pressure (mm Hg)		
Brachial Artery	135/75 $\underline{95}$	140/75 $\underline{100}$
Pulmonary Capillary Wedge	$\overline{25}$	$\overline{28}$
Pulmonary Artery	48/25 $\overline{34}$	47/23 $\overline{37}$
Right Ventricle	48/5	47/6
Right Atrium	$\overline{8}$	$\overline{7}$

through the fistula, recorded directly with an electromagnetic flowmeter, was 140 ml per minute and was retrograde, verifying the angiographic findings. Flow went from the digits of the hand into the fistula. The distal limb of the fistula was ligated. Following operation, the right hand became asymptomatic and the digital ulcerations slowly regressed. Transfusions and subsequent hemodialysis resulted in symptomatic improvement of the congestive cardiac symptoms. Several months after operation unrelenting angina pectoris developed. It continued several hours and the patient died at home. Postmortem examination revealed a recent occlusion of the anterior descending coronary artery, a fresh antero-lateral myocardial infarct, diffuse and severe arteriosclerosis of all coronary vessels, cardiomegaly, a few pericardial adhesions, and small kidneys with little parenchyma.

Discussion

In 1757, William Hunter first described an arteriovenous fistula.[1] His findings and descriptions were verified repeatedly, but it was left to Emil Holman to put the lesion into physiological perspective in the 1920's.[2] It was appropriate for a surgeon like Holman to be interested in such a vascular problem because the majority of fistulas usually develop secondary to trauma. Indeed, the last time this disorder was discussed at Medical Grand Rounds, the case presented was that of an arteriovenous fistula arising as a complication of lumbar laminectomy. This surgical curiosity first fell into the realm of the internist via the nephrologist's need for vascular access in patients requiring chronic hemodialysis. A short lifespan and high rates of infection, hemorrhage, and thrombosis with the Quinton-Scribner cannula led Brescia and co-workers in 1966 to intentionally create a forearm arteriovenous fistula between the radial artery and the cephalic vein.[3] Making use of observations first noted 200 years previously, Brescia realized that this operation would result in greatly dilated forearm veins with high pressures and flow rates, thus meeting the basic requirement for percutaneous hemodialysis—namely, the ready availability of a large blood supply under adequate enough pressures to perfuse the artificial kidney machine. An added benefit was that the blood could be obtained from a venipuncture, thus avoiding the hazards inherent in repeated arterial punctures. In addition, the cleansed blood leaving the kidney machine could be directed back into the patient's vascular system via venipuncture of the large distended forearm veins.

A forearm arteriovenous fistula is now a familiar vascular access route in most hemodialysis units. Moreover, the lives of 5,000 Americans are now being maintained by chronic hemodialysis, and since many of these patients have a subcutaneous fistula, all physicians—not only surgeons—should be aware of the potential complications of this lesion.[4] Today, I shall review the hemodynamics of an arteriovenous fistula of the forearm, emphasizing the alterations of the peripheral and cardiac circulatory systems, and outline the cardiovascular contraindications for creation of such an anastomosis. These observations were made on patients at the Northern California Artificial Kidney Center located at the San Francisco General Hospital.

Blood, like water, follows the path of least resistance. Thus, when the radial arterial blood reaches an arteriovenous fistula, it preferentially flows into the low resistance venous system rather than into the relatively high resistance vascular network of the hand. Since the vein is in direct continuity with the high pressure artery, peripheral venous hypertension results and is especially pronounced at the anastomosis site. High peripheral venous pressure at the time the central venous pressure is low accelerates the flow of blood from the periphery toward the heart. Holman aptly termed this leeching of the arterial blood by the venous blood as a "parasitic circuit" of an arteriovenous fistula.[5] Since the blood destined for the hand and digits never arrives,

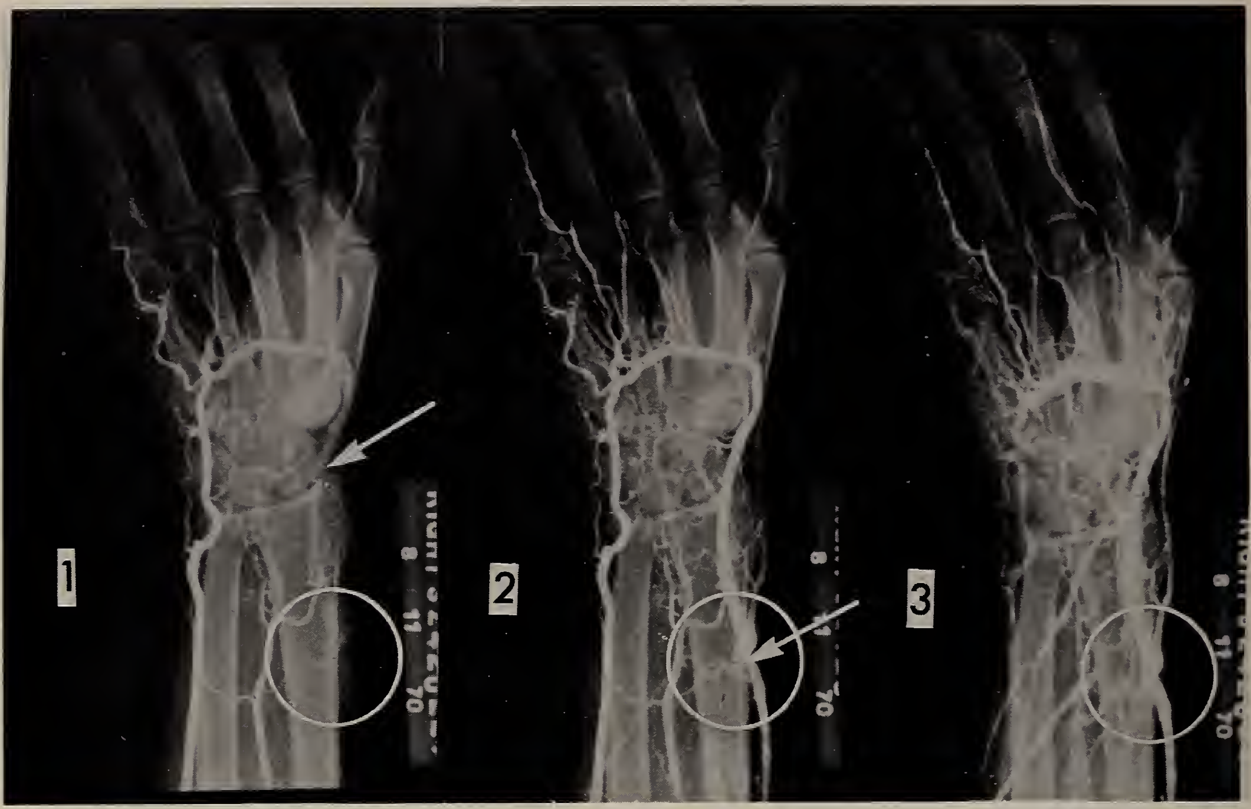

Figure 1.—A brachial arterial angiogram of the right forearm and hand in patient herein discussed. The fistula site is circled. In Frame 1 the ulnar arterial system is opacified; the head of the ulnar arterial blood has traversed the palmar arch and filled the radial artery distal to the fistula site (arrow). There is no filling of the radial artery proximal to the fistula. In Frame 2 the ulnar blood has traversed the distal radial arterial system in a retrograde fashion and opacifies the cephalic vein via the fistula. In Frame 3 (a late film in the series) the radial artery proximal to the fistula has still not opacified.

compensatory mechanisms are triggered, two immediate ones being an increase in cardiac output and an increase in collateral arterial blood supply. The increased venous pressure near the fistula also impairs efflux of blood from the deprived tissues by increasing vascular outflow resistance. However, each compensatory mechanism has its own particular set of problems.

Using noninvasive techniques of plethysmography and ultrasound, we studied blood flow in the forearm and digits and cardiac output responses in over a dozen patients with an arteriovenous fistula. The plethysmographic technique used in our laboratory has been described in detail elsewhere.[6] The results demonstrated that if a forearm arteriovenous fistula is constructed in a side-to-side fashion, the fingers of the fistula hand always have a decreased blood flow although the forearm blood flow is always elevated (Chart 1). Angiographic and oscillometric studies document the mechanism responsible for this fall in peripheral perfusion.[6,7] Blood flow in the ulnar artery normally supplies the lateral aspect of the hand, but the ulnar vessels also have potential communications with the radial arterial network via the superficial and deep palmar arterial arches. An arteriovenous fistula between the radial artery and the cephalic vein lowers the arterial pressure distal to the anastomosis site, namely within the distal radial artery. If the palmar arches are patent, the ulnar arterial blood flows into the low pressure radial arterial bed of the hand and thence, in a retrograde fashion, out of the hand and into and through the low resistance fistula. Thus, a mechanism designed to compensate for a decrease in blood flow is actually "stolen" by the parasitic fistula circuit.

Although most patients with a radial artery-cephalic vein fistula have a subclinical radial fistula steal, some patients have mild symptoms. Occasionally, severe and incapacitating ischemia

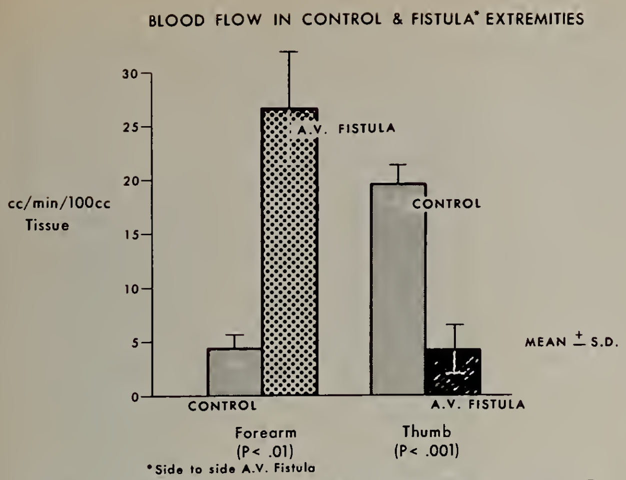

Chart 1.—Blood flow in the forearm and thumb of seven patients with side-to-side radial artery-cephalic vein arteriovenous fistulas. Blood flow in the fistula forearm is four times greater than the flow in the control forearm, reflecting the magnitude of the flow through the fistula. Blood flow in the digits of the hand with the fistula is three times less than the flow in the control hand, reflecting the magnitude of the fistula steal. The differences are statistically significant.

develops, as in the patient presented today. In this patient, pain with use or elevation of the arm, as well as ischemic ulcerations on the thumb and forefingers, documented the clinical importance of the radial fistula steal syndrome. Blood flow to his thumb was one-tenth of control levels, whereas arterial blood flow in his forearm was four times normal, reflecting the size of the arteriovenous communication. This patient was unique in that the entire arterial blood supply to the fistula was from his radial arterial bed and at the expense of the digital blood supply; the radial artery proximal to the fistula was completely occluded. He represents the epitome of the steal syndrome first described by Hurwich.[8]

After clinical, physiological and angiographic documentation of the potential hazards inherent in the side-to-side arteriovenous forearm fistula, the anastomosis is now constructed in the following manner. At the completion of fistula construction, the artery immediately distal to the anastomosis is intentionally sacrificed by ligation. This simple modification of the Brescia operation converts a side-to-side arteriovenous fistula into an end-to-side design. This prevents retrograde blood flow out of the hand and directs the entire ulnar blood flow into the digits. Obviously, preoperative or intraoperative documentation of the patency of the palmar arcade is necessary before sacrifice of the distal radial artery. The entire blood supply of the medial aspect of the hand now comes from arterial blood, which must cross the palmar arches to enter the distal radial arterial vessels. Postoperative plethysmographic blood flow studies in nine patients with an end-to-side anastomosis showed that the fistula flow is comparable to the flow in a fistula of side-to-side design but that blood flow into the digits of the fistula extremity is not decreased.[9] Furthermore a fistula steal complex has never been observed in these patients. Therefore, at present, all arteriovenous fistulas constructed at San Francisco General Hospital are of an end-to-side design. Venous flow measurements have not been performed in our laboratory, but one would expect diminution in blood flow from the fistula hand because the increased venous pressure would impede venous outflow from the hand.[10] Clinically, however, only when the venous outflow branch from the fistula to the arm suddenly becomes occluded have problems arisen. Fortunately, this developed in only one instance. Angiography demonstrated that the entire fistula flow was directed retrogradely into the dorsal veins of the hand, resulting in severe pain and edema. Emergency closure of the fistula was performed.

A large arteriovenous fistula results in a fall in systemic blood pressure and an increase in venous return to the heart, thus increasing the cardiac stroke volume, the heart rate, and the cardiac output.[11] The changes in cardiac output and heart rate parallel increases in fistula flow when the arteriovenous communication is large. In 1875, Nicoladoni[12] first described a fall in heart rate with compression of an arteriovenous fistula. In 1890, Branham[13] rediscovered the sign and speculated that it was mediated by the vagus nerve, a fact substantiated by Sir Thomas Lewis[14] when he obliterated the bradycardia by injections of atropine. Indeed, slowing the heart rate by temporary manual occlusion is a reliable bedside method of estimating the size of a large fistula.[15] Since fistula blood flow is a direct function of both the size of the vessel supplying it and the diameter of the communication itself, the greatest hemodynamic changes occur when the aorta is involved; cardiodynamic measurements are less altered when the femoral or axillary vessels feed the anastomosis. Fistulas involving vessels the size of the radial or ulnar arteries have the least effect on the heart. The effect of a forearm arteriovenous fistula on heart rate and cardiac output have been reported by several dialysis centers.[16-18] The indicator dilution method or the Fick oxygen technique is usually employed, necessitating cardiac catheterization. We use the noninvasive ultrasonic technique to determine cardiac output in our patients.

Ultrasonic techniques, an outgrowth of wartime sonar, were introduced into clinical medicine to evaluate cardiac disease over a decade ago.[19] The technique has been used extensively for diagnosing pericardial effusions, mitral valve dysfunction, and intracardiac masses, as well as for documenting the presence of intracardiac shunts and hypertrophic subaortic stenosis.[20-23] Feigenbaum[24] first proposed that the method be used to determine left ventricular stroke volume. Briefly, the ultrasonic transducer is placed on the external surface of the anterior chest wall and the hand-held transducer beam is directed toward the left ventricle. Continuous monitoring of the returning signal on an oscilloscope enables the operator to locate the anterior and posterior endocardial surfaces of the left ventricle; the resultant image is captured on polaroid film. To determine ventricular volume, the ventricle is assumed to be similar to a prolate ellipse and measurements taken from the film in systole and diastole are cubed to obtain end-systolic and end-diastolic volumes.[25] The difference in volumes multiplied by the heart rate equals the calculated cardiac output. Although applicable in only 60 to 70 percent of patients and yielding only qualitative information, the method has deservedly found a place in clinical investigation. Repeated cardiac catheterizations in our patients would be impractical. We have obtained satisfactory cardiac output measurements in eight instances from seven of ten patients: In one patient, measurements were obtained both before and after removal of a Scribner shunt, and in three other patients satisfactory ultrasound records of ventricular volumes could not be obtained although their heart rate responses were included in the analysis (Chart 2). Ventricular volume and heart rate were measured when the forearm arteriovenous fistula (and cannula) were open and then immediately after manual compression of the anastomosis. A fall in heart rate was considered significant if the rate immediately after compression was ten beats slower than the initial rate. A fall in cardiac output was considered significant if there was at least a 15 percent change between initial and final determinations. Similar to studies employing cardiac catheterization and direct Fick oxygen technique, there was a fall in cardiac output and heart rate immediately after compression of the forearm arteriovenous fistula, although the changes were not statistically significant.[18] In addition, fistula blood flow was measured by plethysmography in all patients, and shunt flow was measured by a cuff-type ultrasonic flowmeter in two patients who also had a Scribner cannula. Even though directly measured, flow through the forearm fistula never contributed more than 15 percent to the total cardiac output in any of our patients and the change in cardiac output with fistula compression was small. We believe, however, that even if small these fistulas do place an additional hemodynamic burden on the heart. The resting cardiac output values are high but reflect the anemia of uremia rather than a hyperkinetic circulation owing to the fistula.[26]

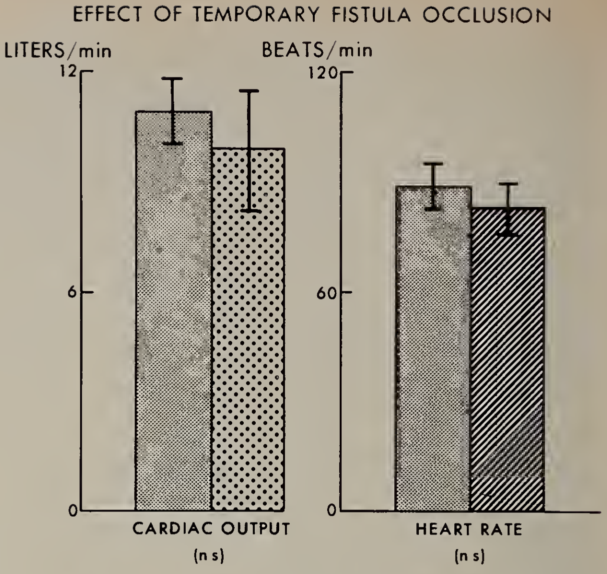

Chart 2.—Cardiac output and heart rate changes in seven patients with forearm arteriovenous fistulas before (left) and after (right) manual compression of the fistula. Cardiac output and heart rate tended to fall during compression, but the differences are not statistically significant.

A small arteriovenous fistula causes an additional hemodynamic burden on the heart, but it is modest and probably inconsequential in the patient who has no cardiac abnormalities. Studies with heart-lung preparations and metabolically supported hearts *in vitro* show that increasing cardiac work by alternating blood flow is accompanied by a relatively slight increase in myocardial oxygen consumption.[27] This means that in the heart of a patient with an arteriovenous fistula, a great deal of extra work can be performed without decreasing cardiac efficiency. Only when coronary perfusion is compromised, particularly in the setting of poor sympathetic support, has it been possible to systematically elicit "high output" cardiac failure.[28] Cardiac output in both man and experimental animals with heart failure due to an arteriovenous fistula is normal but cardiac filling pressure is elevated. In the patient presented today, severe and diffuse underlying coronary arteriosclerosis was manifested clinically and documented pathologically. The minor hemodynamic burdens of the arteriovenous fistula and Scribner shunt no doubt contributed to the patient's congestive heart failure.[6] Congestion was verified by the elevated left ventricular filling pressures but the cardiac index was low for a hyperkinetic state. The lack of significant change in cardiac output on fistula compression and further elevation in pulmonary capillary wedge pressure reflect the myriad factors contributing to the heart failure.

Because of experiences with patients like the one discussed today, we believe that angina pectoris, previous congestive heart failure, uremic myocardiopathy and other forms of heart disease are relative contraindications for the placement of an arteriovenous fistula in a patient receiving chronic hemodialysis. The history of angina pectoris seven years before fistula construction may have been the clue against performance of the fistula type of operation. In patients who require chronic maintenance hemodialysis we prefer the Scribner shunt, as the flow through the cannula can be better controlled and more conveniently monitored (cuff-type flow-meters).

I have not discussed the longevity of an arteriovenous fistula, but our clinical and laboratory experience shows that larger fistulas remain open the longest and have flow rates more satisfactory for chronic maintenance hemodialysis. Similar observations have led other investigators to construct larger fistulas, which of necessity means larger diameter arteries and thus more centrally located fistulas.[29] A saphenous vein loop placed in the femoral area is becoming an increasingly popular means of increasing the fistula usefulness and longevity. However, the centrally placed fistulas are potentially more dangerous, and a large increase in cardiac output while arterial blood pressure is low, especially in a patient receiving antihypertensive medications, may be an ideal model for producing cardiac decompensation even if the heart is normal. To date, we are still reluctant to use the femoral vessels for construction of such a fistula.

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Important Advances in Clinical Medicine

Epitomes of Progress -- Anesthesiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Anesthesiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Anesthesiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Anesthesiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102

Muscle Relaxants

Recent experimental and clinical studies greatly increased our understanding of the influence of various factors on the pharmacological effects of muscle relaxants. This new information markedly influenced the choice and mode of administration of available muscle relaxants and the search for better ones.

It was observed that the prolonged administration of depolarizing relaxants may cause desensitization of the neuromuscular junction and difficulties in the postanesthetic reestablishment of neuromuscular transmission. It was also demonstrated that the decreased rate of metabolic transformation of succinylcholine by inherited abnormalities of plasma cholinesterase and other pathological changes (for example, liver disease) or the intentional or accidental administration of anticholinesterases may cause prolonged postoperative apnea. In infants, in severely burned or traumatized patients, and in the presence of certain neurological conditions (for example, paraplegia), succinylcholine may cause severe arrhythmias or even cardiac arrest.

Because of the possibility of such difficulties, there has been an increasing tendency to provide surgical relaxation with nondepolarizing relaxants. The presently available nondepolarizing agents [for example, d-tubocurarine chloride; gallamine triethiodide (Flaxedil®)], however, lack the controllability of succinylcholine and may also have undesired effects. Two other nondepolarizing agents, diallylnortoxiferine chloride (Alloferine®) and pancuronium bromide (Pavulon®), are relatively free of unwanted side effects. It is expected that pancuronium will be available for clinical use in the near future.

Francis F. Foldes, M.D.

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Foldes FF, Klonymus DH, Maisel W, et al: Studies of pancuronium in conscious and anesthetized man. Anesthesiology 35:496-503, Nov 1971

Recent Advances in Obstetric Anesthesia

The most important recent advances in obstetric anesthesia are not the new drugs or techniques that have been introduced to provide better analgesia. Rather, they are the major modifications of older established techniques with a view toward preventing serious anesthetic complications such as maternal hypotension and aspiration pneumonitis.

Maternal hypotension may occur in as many as 80 percent of parturients following regional anesthesia for cesarean section. However, with aggressive prophylactic measures the incidence decreases to less than 15 percent. Hypotension is due to a combination of sympathetic blockade and compression of the vena cava by the gravid uterus. Anticipating sympathetic paralysis, many anesthesiologists routinely administer a liter of lactated Ringer's solution intravenously and ephedrine 50 mg intramuscularly within 20 minutes of the block. Immediately following the block and before operation, the uterus is displaced off the inferior vena cava. Left uterine displacement is most easily and successfully accomplished with the use of a mechanical device attached to the surgical table. If such an apparatus is not available, a small pillow placed under the right hip, together with lateral tilting of the surgical table, occasionally is effective in producing left uterine displacement. Should hypotension occur, recent studies have indicated that vasopressors such as ephedrine, Wyamine® or Aramine® are effective in restoring uterine blood flow following spinal hypotension. Pure vasoconstrictor drugs such as Vasoxyl® or Neosynephrine® should be avoided, as these drugs, although restoring the blood pressure, produce further decreases in uterine blood flow with subsequent fetal hypoxia and acidoses.

Aspiration pneumonitis is most easily prevented by avoiding general anesthesia. However, if general anesthesia is used, many anesthesiologists routinely protect the airway of the patient by endotracheal intubation. Because regurgitation or vomiting may also occur during intubation or extubation of the trachea, the following prophylactic techniques are being used with increasing frequency. Before induction of anesthesia (up to 2 hours) one ounce of oral antacid is administered. Maternal gastric pH will immediately rise above dangerous levels. If the patient is awake, intubation is not appropriate, and extremely rapid ("crash") induction of anesthesia is performed with intravenous thiopental and succinylcholine. Because muscular fasciculations caused by succinylcholine may be associated with increased intragastric pressure and a greater tendency for the patient to regurgitate, a 3 mg dose of curare is given 5 minutes before induction of anesthesia. An assistant applies cricoid pressure to compress the esophagus before and during endotracheal intubation. The endotracheal tube is left in place until the patient awakens; she is placed on her side in the head down position, and with suction apparatus immediately available, the endotracheal tube is removed.

One of the greatest tragedies in medicine is death of a mother during childbirth. Complications of anesthesia account for up to 10 percent of all maternal deaths. Many of the deaths might be preventable by use of prophylactic techniques which have been discussed.

Sol M. Shnider, M.D.

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James FM, Greiss FC, Kempra: An evaluation of vasopressor therapy for maternal hypotension during spinal anesthesia. Anesthesiology 33:25-34, Jul 1970

Shnider SM, deLorimier AA, Asling JH, et al: Vasopressors in obstetrics: Fetal hazards of methoxamine administration during obstetric spinal anesthesia. Am J Obstet Gynecol 106:680-686, Mar 1, 1970

Halogenated Anesthetic Agents

The current status of halogenated anesthetic agents is best characterized by the term "unsteady state." While much new information is being gathered concerning safety and toxicity, the utilization of the agents at any given time seems to be a result of the forces of experience, emotion and fear of malpractice. The agents still remain an important mainstay of inhalation anesthesia.

Halothane continues to be widely used. Since its introduction in the late 1950's it has provided pleasant and safe anesthesia for millions of patients. The agent offers great flexibility, it is not unpleasant to smell, it is non-explosive, the incidence of nausea and vomiting is small, high concentrations of oxygen can be used. These are real and important advantages to physician and patient. In spite of considerable looking no one has found this drug to possess a higher mortality or morbidity rate than any other widely used approach to anesthesia for major operation.

The occurrence of "hepatitis" associated with use of halothane is apparently real. The most popular opinion is that this results from sensitization. Evidence for sensitization is its low incidence (one in thousands), lack of dose dependence, apparent increased incidence and rapidity of recurrence with repeated halothane use and failure to produce the lesion in laboratory animals. There is some recent evidence from chronic exposure at very low dosage, however, which suggests sensitization may not be the only factor responsible for hepatic injury.

Fluroxene has never been widely popular. In recent years evidence revealing higher values for blood pressure, cardiac output and alveolar ventilation has resulted in increasing use of this drug. There are now reports of hepatitis occurring with fluroxene, and the agent is explosive in the anesthetic range. Nausea and vomiting appear to be more common than with halothane. There are no data which relate the higher cardiorespiratory values to improved patient welfare, and this drug, which has been on the market for many years, does not appear to be headed for great popularity.

Methoxyflurane has been rather definitely associated with high output renal failure. Unlike the hepatic lesion of halothane, this lesion, available evidence in humans and laboratory animals suggests, is a reproducible, dose-dependent toxic protoplasmic effect. Low vapor pressure and high solubility are at once advantages and disadvantages of the agent. They do reduce its flexibility and versatility. As a result of this and the renal toxicity, methoxyflurane appears to be diminishing in clinical usage and importance.

Perhaps the most important aspect of the current status of these agents is the realization that they are metabolized to a large extent. Not many years ago, inhalation agents were thought to be excreted unchanged via the lungs. Now biodegradation is known to occur in surprisingly large fractions of the dosage administered. Metabolites or altered metabolic activity may explain much of the toxicity, idiosyncracy and species variability which has been characteristic of the evaluation of anesthetic agents over the years.

Suggestions have been made that contamination of operating room atmospheres may be responsible for abortions, hepatitis and perhaps other untoward events affecting operating room personnel. Without debating the validity of such claims, there is no firm evidence that halogenated agents are the important offenders.

William K. Hamilton. m.d.

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Eger EI II, Smith NT, Cullen DJ, et al: A comparison of the cardiovascular effects of halothane, fluroxene, ether & cyclopropane in man. Anesthesiology 34:25-41, Jan 1971

Dissociative Anesthesia

The need has been great for a method of producing analgesia and amnesia in patients for short periods of time without depressing respiration and circulation. To date ketamine is the best answer to this need since its use is characterized by catalepsy, amnesia and analgesia. The state has been designated as dissociative anesthesia since the patient truly seems disassociated from his environment. During this state blood pressure and pulse rate are more likely to be elevated than depressed. Minute volume of respiration usually is not decreased to a significant degree unless too large a dose is given too rapidly. Pharyngeal and laryngeal reflexes usually remain active enough to protect against aspiration of foreign material into the tracheo-bronchial tree.

Ketamine (Ketaject,® Ketalar®) is not the perfect agent and undoubtedly more satisfactory drugs will become available for production of dissociative anesthesia. In some patients blood pressure elevation following administration of ketamine may be alarming. A few patients exhibit an excitement stage during induction and a greater number exhibit psychomotor activity during recovery that may require medication with phenothiazine, diazepam or barbiturate. The greatest deterent to the widespread use of ketamine has been the unpredictable unpleasant dreams that about 15 percent of patients experience during recovery. These can be diminished, but not predictably eliminated, by protection of the patient from undue sensory stimulation during recovery and the use of sedatives as discussed above.

At present the same precautions for monitoring and patient care must be available during dissociative anesthesia as during other conventional types of anesthesia.

JOHN W. PENDER, M.D.

REFERENCE

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New Halogenated Anesthetics: Enflurane and Isoflurane

Two new halogenated ethers, enflurane (Ethrane,® $CHFCl\ CF_2\text{-}O\text{-}CF_2H$) and isoflurane (Forane,® $CF_3\ CHCl\text{-}O\text{-}CF_2H$), are undergoing intensive studies with an eye toward introduction into clinical practice. They possess their own merits and offer reasonable alternatives to currently available inhalational anesthetics. The latter is important because of concern about flammability or toxic effects of various accepted agents. Enflurane has received fairly broad clinical use whereas isoflurane is undergoing intensive clinical trials.

Since their chemical structures are so alike one might expect similar properties. They possess similar, relatively low solubility in blood and lipids, are nonflammable and are highly stable in the bottle and in the presence of alkali. Both preserve myocardial function and cause vasodilatation. The latter predominates so that arterial pressure is generally less than awake values in the unstimulated subject. Respiratory depression occurs with both to a degree as great as or greater than available agents. Both depress neuromuscular function. Isoflurane is more depressant to neuromuscular function by itself or in combination with neuromuscular blocking agents than halothane. Relatively small doses of muscle relaxant drugs are needed to provide adequate surgical conditions.

Despite similar physical characteristics enflurane and isoflurane differ significantly in their effects. Isoflurane is less susceptible to biodegradation than enflurane. Isoflurane's lack of metabolism makes it unique among halogenated anesthetics and may make its highly halogenated nature less worrisome. Enflurane sensitizes the myocardium to the arrhythmic effects of epinephrine but isoflurane does not. Both agents induce prominent EEG burst suppression. However, enflurane anesthesia is characterized by increasing EEG wave frequency as anesthetic dose increases, by high voltage spikes and, occasionally, by seizure patterns. Muscle twitches and muscle seizure activity have occurred. The muscle activity usually signifies presence of relatively deep anesthesia or hypocarbia or both and can be stopped by reversal of the latter events. The central nervous system effects are not associated with cerebral ischemia or injury. This innocuousness lends credence to the view that enflurane's EEG effects, although somewhat unique, are in the spectrum of normal anesthetic effects.

WENDELL C. STEVENS, M.D.

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Patient Monitoring

The standard vital signs of blood pressure, pulse, respiration and temperature have been valuable in assessing patients' conditions and problems for many decades. With modern electronics, the electrocardiogram has been a useful addition to the constant monitoring of patients, especially in detecting arrhythmias early and establishing therapy or preventive maintenance. The electroencephalogram has been a disappointment because of the difficulties with artifacts such as muscle activity and electrical interference. The hopes that it would provide an early warning system of problems of cerebral circulation and blood gas abnormalities also have proved unfounded.

The Doppler apparatus or ultrasonic monitoring of circulation has been extremely useful in evaluating a number of conditions.[1] An additional use is the "immediate detection" of air embolism by placing the probe over the heart during operations in which this complication may occur.

Recent advancements in electrical systems have provided sophistication in continuous temperature monitoring. Probes are available for surface, esophageal, rectal or intramuscular and intradermal temperature. They may be presented either on a meter or in actual digits. Digital display has also been perfected for display of cardiac rate and other physiological functions where the actual wave forms are unimportant. This speeds the assessment of vital signs for physician and nurse.

The advance in knowledge of strain gauges and their calibration and balancing has led to a whole new area of monitoring. With their use, the continuous presentation of arterial or venous blood pressure has become increasingly common, especially now that the recent invasion of the arterial system through radial artery puncture has become a common procedure with few complications. These pressure transducers are also used in pneumotachographs which may be used for monitoring respiratory flow rate curves and integrated to read in tidal or minute volumes.

The advent of solid-state circuitry for compactness and stability of electronic equipment and simplification of controls and application of such instruments has enabled physicians with little knowledge of electronics to use them more easily and correctly. In order to be truly useful, monitoring devices must be simple to operate, easy to apply and remove, and relatively free of artifacts and maintenance problems. It is most important that they must not present problems of maintenance or hazard lest attention be diverted from the patient.

The electrode methods of determining blood gases and pH and the flame photometer for sodium and potassium have provided us with extremely valuable and rapid information for management of patients with a wide range of abnormalities of acid-base and fluid-electrolyte balances. The availability of these methods of rapid chemical determinations on small quantities of blood depends a great deal on provision of adequate space and personnel to perform these functions. The facilities should be near to the areas where patient care requires this information —operating rooms, recovery rooms, and intensive care areas.

Biomedical technicians and biomedical equipment technicians to perform these tests and to maintain proper monitoring environment have come into great demand and are a necessity to the fields of acute and sub-acute medical care mentioned above. Efforts are under way to provide such personnel with adequate training in physics and engineering and in how to function within the special demands of a hospital and patient care. Since the new monitoring equipment presents definite electrical hazards to the patient, such technicians as well as nursing personnel and physicians must be thoroughly trained as to precautions. Excellent articles regarding these hazards have been published by the Association for the Advancement of Medical Instrumentation. They are highly recommended to all persons involved with electronic monitoring in any form.[2]

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Local Anesthetics and Regional Anesthesia

Some of the most important advances in local anesthetics in the recent past include: (a) apparent selective barrier to placental transfer of local anesthetics shown to result from differences in drug binding to maternal and cord plasma proteins;[1] (b) fetal bradycardia following paracervical block shown to be associated with high fetal levels of local anesthetic, derived by transmural diffusion of drug into arteries directly supplying the placenta,[2] and (c) favorable pharmacokinetic properties of bupivacaine, with respect to other anilides, have been demonstrated as exemplified by the decreased potential for systemic accumulation during continuous techniques.[3]

In regard to technique, the "pure" secondary effects of peridural anesthesia have been firmly established with human volunteer studies.[4,5,6] These studies have shown that in normal, unmedicated man, the circulatory effects are influenced by: (1) the number of vasomotor segments interrupted; (2) whether or not cardiac sympathetics are blocked; (3) direct and indirect action of the local anesthetic on the heart; (4) cardiovascular effects of epinephrine; and (5) the condition of the patient. In normal man, block as high as T2-3 does not produce significant circulatory changes. Local anesthetics have been shown to have a direct depressant effect and indirect chronotropic effect through stimulation of sympathetic centers in the brain. The net effect depends on the arterial blood levels: Injection of large single doses, or several repeated doses, results in arterial blood levels of 4-7 μg per ml, which produce sufficient stimulation of sympathetic centers to counteract the direct depressant effect, resulting in an increase in heart rate, in cardiac output and in mean arterial pressure. Excessive doses produce enough direct myocardial depression to offset the stimulating action, resulting in decrease in cardiac output and arterial pressure. Epinephrine absorbed from the peridural space produces a beta adrenergic stimulating action reflected by an increase in cardiac output but a pronounced decrease in total peripheral resistance, with a net effect of decrease in mean arterial pressure. These studies further showed that in normal man removal of a modest amount of blood (10 ml per kg of body weight or 13 percent of blood volume) makes the subject highly vulnerable to extensive vasomotor blockade and the direct depressant effect of the local anesthetic used for high peridural block.

John J. Bonica, m.d.

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2. Asling JH, Shnider SM, Margolis AJ, et al: Paracervical block in obstetrics. II. Etiology of fetal bradycardia following paracervical block in anesthesia. Am J Obstet Gynecol 107:626, Jun 1970

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Emergency Outpatient Anesthesia

The basic concept for outpatient surgical operations under general anesthesia is that the administration of an anesthetic today does not of itself require hospitalization. The patient to whom the anesthetic is to be given and the nature of the proposed operation are the limiting factors.

It is essential that the outpatient be as carefully evaluated for anesthesia as if he were an inpatient. This can be done with the cooperation of the surgeon in the selection of the type of patient, and by immediate pre-anesthetic evaluation of all patients by an anesthesiologist.

Operative procedures are limited to those in which post-operative bleeding is highly unlikely. Hence tonsils and adenoids are not accepted. Plastic procedures, examinations under anesthesia, including a diagnostic dilation and curettement, cystoscopy, and peritoneoscopy are all done. Herniorrhaphy on a child is acceptable.

No patient is permitted to leave the outpatient recovery area unless accompanied by a responsible adult. By use of care in the selection of patients and with full cooperation of surgeons, many procedures have been provided patients at less cost and with use of fewer hospital beds. Ten years' experience indicates that outpatient surgical operation under general anesthesia is practical, economical and provides a health care service to many patients who might otherwise not be treated.

John B. Dillon, m.d.

REFERENCE

Cohen D, Dillon JB: Anesthesia for Outpatient Surgery. Springfield, Ill, Charles C. Thomas Inc., 1970

Psychedelic Drugs and Anesthesia

There is very little information in the recent medical literature regarding the effects of anesthetic agents on patients who abuse psychedelic drugs.

In one excellent study, Jonston et al reported the effects of acute and chronic administration of

D-amphetamine on halothane requirements in dogs. Acute intravenous administration of dextroamphetamine during halothane anesthesia caused pronounced dose-related increases in blood pressure, body temperature, anesthetic requirement and, in 12 of 15 animals, cardiac arrhythmias.

Dogs treated with dextroamphetamine 2.5 mg per kg of body weight intramuscularly twice daily for one week immediately before being anesthetized showed significantly *decreased* anesthetic requirements, and no change in blood pressure, body temperature or cardiac rhythm.

These chronically treated animals also showed decreased responsiveness to an indirectly acting vasopressor (tyramine).

These apparently contradictory results may be explained by acute release, followed by depletion of, catecholamine stores.

Anesthetic management of patients using hallucinogens is further complicated by the fact that ingestion of combinations of stimulant and depressant drugs in unknown ratios is the rule.

The only appropriate generalization regarding anesthetic management of these patients is that it must be individualized.

RICHARD BARBER, M.D.

REFERENCE

Jonston RR, Way WL, Miller RD: Alteration of anesthetic requirement by amphetamine. Anesthesiology 36:357-363, Apr 1972

Pediatric Anesthesia

Recent measurements show that children and especially infants differ from adults not only anatomically and physiologically but also in drug tolerance, anesthetic requirement and rate of anesthetic uptake.

Increased neonatal survival in correction of diaphragmatic hernia, cardiac defects and intestinal obstruction now follows preoperative acid-base correction, refined anesthetic techniques and subsequent ventilatory support.

Explosive anesthetics are generally replaced by halothane or combined intravenous agents, and modified T-tube inhalation apparatus predominates. Monitoring by stethoscope is mandatory, and of blood pressure with Doppler sensor and of temperature with thermistor highly advisable. Extremes of hypothermia and hyperthermia have proved fatal unless controlled promptly.

Since the puzzling anesthetic deaths in burned children have been traced to widespread potassium release from damaged muscle following succinylcholine, this agent is avoided in conditions involving denervated muscle.

Improved methods now reduce fear, unnecessary injections and prolonged hospitalization, and facilitate increased operations on out-patient basis, with obvious emotional and financial benefit to patients.

ROBERT M. SMITH, M.D.

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Britt BA, Kalow W: Hyper-rigidity and hyperthermia associated with anesthesia. Ann NY Acad Sci 151:947-958, Jul 1968

Anesthesia for Intracranial Operation

Recent studies concerning the effects of a variety of anesthetics on cerebral blood flow (CBF) and intracranial pressure (ICP) have largely resolved the controversy concerning the selection of anesthetic agents for patients with intracranial disease. Barbiturates and narcotics (including the combination of droperidol and fentanyl (known as Innovar®) reduce CBF and ICP both in normal man and in patients with intracranial mass lesions, and on this basis are excellent choices for induction and maintenance of anesthesia. The new dissociative drug ketamine produces large increases in CBF and ICP and should be avoided in any patient who might have an intracranial mass lesion. In patients who have had an air contrast study, nitrous oxide (N_2O) will cause increases in ICP because of the rapid equilibration of N_2O with the intraventricular air. The use of halogenated inhalation anesthetics (particularly halothane) is still somewhat controversial. Clearly in the absence of hypocapnia, these anesthetics can cause striking increases in ICP, presumably because of an increase in CBF. However, it was recently shown in a study of patients undergoing intracranial operation that if adequate levels of hypocapnia are established ($PaCO_2$ below 30 mm of mercury) the subsequent administration of halothane does not cause any significant rise in ICP. Thus, if used judiciously and if preceded by hyperventilation, halogenated anesthetics would appear to be safe to use during intracranial operation.

JOHN D. MICHENFELDER, M.D.

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Adams RW, Gronert GA, Sundt TM, et al: Halothane, hypocapnia, and cerebrospinal fluid pressure in neurosurgery. Anesthesia (In Press)

Recent Advances in Respiratory Therapy

Respiratory therapy (formerly called inhalation therapy) continues to advance in the broad areas of training and organization, equipment and techniques. For medical directors of respiratory therapy the California Thoracic Society provides a forum to air common concerns.

There are continuing developments in equipment such as in-line or in-isolette oxygen monitors, improved pressure alarm systems, low pressure endotracheal tube cuffs and disposable nebulizers without a clearly superior model evident. A durable self-inflating resuscitation bag which will give a high oxygen concentration is yet to be found, although many types are marketed.

Among the most useful newer techniques, positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) raises the arterial oxygen in many patients with acute respiratory failure. CPAP is especially effective in treating idiopathic respiratory distress of the newborn.

Methylprednisolone (Solumedrol®), 30 mg per kg of body weight, appears to be the most effective steroid for treating "shock lung."

Sepsis, however, remains the most lethal complication of acute respiratory failure. Acetic acid and copper have antibacterial effects which might minimize environmental infection hazards while maintaining nutrition in the critically ill.

KENNETH W. TRAVIS, M.D.

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Gergory GA, Kitterman JA, Phibbs RH, et al: Treatment of the idiopathic respiratory distress syndrome (IRDS) with continuous positive pressure breathing (CPAP). N Engl J Med 284:1333-1340, Jun 17, 1971

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EDITORIAL

The Health Sciences Bond Issue

PROPOSITION 2 ON THE NOVEMBER 7 ballot would authorize a bond issue to provide health science facilities for the University of California to help meet present and anticipated future needs. This bond issue has the whole-hearted support of the Council of the California Medical Association and President Jean Crum urged its passage in these columns last month. Information with respect to exactly what this bond issue would authorize is to be found elsewhere in this issue. It is to be noted that each project authorized will still require final approval by the legislature.

It is appropriate to recall that the people of California through their legislature mandated the expansion of University of California programs in the health sciences for which the funds are now being asked. This was done after careful study of present and projected needs. The basic facts are well known. Health and health care are growing propositions in our society. The percentage of the gross national product devoted to these purposes is steadily rising. As knowledge in health science increases there is more to be done for more people, and more health professionals of all kinds are needed. And there is no lack of young people who are seeking careers in these professions. The qualified applicants in California and elsewhere far exceed the number that can be accepted.

A sad and disturbing fact is that instead of training its own (or giving its own the opportunity to be trained) the State of California imports 70 percent of its physicians, more than half its dentists, and high percentages of other health professionals. And this is not all. In the nation as a whole approximately 35 percent of the newly licensed physicians each year are foreign medical graduates, and it is also sad and disturbing that there is good reason to believe that many of these are inadequately trained by American standards. California of course has its share of them. Thus California seems unduly, and perhaps even inexcusably, dependent upon other states and foreign nations for the education and training of most of its health personnel, when there are young qualified Californians who are eager to enter these professions, and to get their education and training right here in this great and comparatively affluent state.

We agree that Proposition 2, the Health Sciences Bond Issue, should be passed and that all physicians should support it. But physicians, dentists and even all the health professionals together cannot pass this bond issue alone. What is needed is for each one of us to convince several others outside of our professions to vote for Proposition 2. This is what can make all the difference in what may be a close vote. We must do this. Informational materials are available from CMA* and from local citizens committees. What is done right now is critically important. The November 7 ballot will simply count the votes. We must win this one.

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*For these materials, write to Division of Communications, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

The Rational Approach to Antimicrobial Therapy

ELSEWHERE IN THIS ISSUE of CALIFORNIA MEDICINE, Dr. E. Jack Benner presents a practical approach to antimicrobial therapy. His article contains excellent information on three major classes of antimicrobial drugs—penicillins, cephalosporins and aminoglycosides. The concept of employing a relatively small armamentarium that one can know really well is a good one. And it is certainly true that most of what is new in the antibiotic field involves the above three groups of drugs. Hence Dr. Benner's review is quite appropriate. While it is true that the penicillins, cephalosporins and aminoglycosides would provide excellent therapy for most infections encountered in the usual practice, there are important uses for several other types of antimicrobial agents. In the patient with significant allergic sensitivity to penicillin, cephalosporins would not be safe to use. In a patient of that kind, erythromycin or clindamycin would be good choices for infections due to pneumococci or Group A beta-hemolytic streptococci, vancomycin and clindamycin (susceptibility tests necessary here) for staphylococcal infections, the tetracyclines for Haemophilus influenzae infection or gonorrhea, and tetracyclines or erythromycin for syphilis and Mycoplasma infections. In the above types of infections, of course, the agents listed would often be suitable for primary therapy in a non-allergic patient. For Bacteroides fragilis (by far the most common organism in anaerobic infections), chloramphenicol is currently the drug of choice. Drugs which also look excellent for this type of infection (and for many other anaerobic infections) but which are not yet approved by the FDA for this purpose include clindamycin and metronidazole. For uncomplicated urinary tract infections, many would prefer to use sulfonamides as a first choice. Nitrofurantoin and nalidixic acid are very useful here also, and they have a much broader spectrum of activity against urinary tract pathogens than do the sulfonamides. These agents have an outstanding advantage in that they do not modify the normal bacterial flora of the patient.

Various workers in infectious diseases have different feelings regarding drugs of choice and frequently the differences are probably not really significant. This writer would leave out cephaloglycine now that cephalexin is available, would add phenethicillin (Syncillin®) as an alternative to phenoxymethyl penicillin (with no preference), would add dicloxacillin (Dynapen®) as an alternative tocloxacillin, and hetacillin (Versapen®) as another ampicillin derivative. Among the parenteral preparations, methicillin (Staphcillin®) and oxacillin (Prostaphlin®) should be added as excellent drugs for the management of infections due to Staphylococcus aureus.

The question of significance of bactericidal activity of antibiotics is raised. It is this writer's opinion that such activity is not established as being important except in bacterial endocarditis. In theory, bactericidal effect should also be important in situations in which host defense mechanisms are not effective.

The principles of proper antimicrobial therapy stressed by Dr. Benner deserve careful attention. Some additional principles might be mentioned. It is crucial that the clinician determine, to the best of his ability, whether or not an infection is actually present and that he obtain appropriate cultures before embarking on a course of therapy. Many non-infectious conditions may cause x-ray shadows resembling, for example, those associated with pneumonia. Care must be taken in interpretation of bacteriologic results. For example, potential pathogens such as S. aureus or Pseudomonas aeruginosa may be present in sputum without any significance, as a result of colonization of the upper respiratory tract. Hence the clinician must analyze all the clinical and bacteriologic data carefully in assessing the need for therapy. As suggested earlier, other things being equal, one should always choose an antimicrobial agent which modifies the host's normal flora to the least possible extent in order to minimize the possibility of superinfection.

With regard to the aminoglycosides, the clinician should be alert to certain early warnings which may suggest the likelihood of ototoxicity in patients receiving these drugs. These are (1) presence of factors predisposing to ototoxicity (older age group, impaired renal function, impaired hydration, previous cochlear damage, previous or concurrent use of another ototoxic agent, particularly if it is also nephrotoxic, and excessive dosage or duration of therapy), (2) worsening of renal function, (3) excessive blood levels of drug, (4) tinnitus, (5) fullness in ears, (6) high frequency audiographic changes, and (7) early evidence of vestibular or auditory loss. Serious ototoxicity may often be avoided if the offending drug can be discontinued (or dosage reduced) when some of the above warning signs are first noted.

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Reducing the Toll from Sudden Death

SUDDEN CARDIOVASCULAR COLLAPSE AND DEATH, usually due to coronary artery disease, is a public health problem of enormous magnitude. Of the 700,000 deaths each year in the United States from coronary disease, almost 70 percent occur in patients who die before reaching a hospital. Many of these deaths are virtually instantaneous, unwitnessed, and entirely unexpected.[1]

During the past several years increasing attention has been directed toward development of practical and effective mechanisms for reducing the sudden death toll. The contribution by Dr. Lewis and his associates in this issue of CALIFORNIA MEDICINE delineates several aspects of one approach to the overall problem. Their pilot study confirms the efficacy of paramedical personnel training similar to that advocated by Nagel and co-workers[2] and indicates that, with adequate impetus from concerned physicians, legislative action can be initiated sufficient to limit the liability of medical and paramedical personnel dealing with sudden death. In addition, it underscores the need for codification and implementation of standards for training paramedical personnel manning mobile units and for judging their competence. Since at least 6,000 physicians would be required for "flying squads" for countrywide utilization of physician-staffed units,[3] results of this pilot study reaffirm the economic advantage that might result from utilization of paramedical personnel and mobile equipment already available in the community.

Nevertheless, the potential value of mobile intensive care units must be considered in the context of the overall problem of sudden cardiovascular collapse and death and in the light of extensive experience in coronary care units. At first blush the efficacy of coronary care units in reducing mortality from approximately 35 percent to 20 percent[4] is encouraging. This salvage reflects prompt, effective treatment of "primary" ventricular fibrillation and, even more importantly, pharmacologic stabilization of cardiac rhythm well enough to preclude development of lethal ventricular dysrhythmias. Most coronary care unit mortality now results from power failure—a syndrome reflecting necrosis of a critical mass of myocardium.[5] However, only approximately one-third of patients who die from coronary artery disease reach a hospital and since only 50 percent of those are salvageable currently, the total impact of coronary care units on mortality is unfortunately quite limited.[1]

In general, patients fail to reach the hospital alive because death often occurs so quickly, because patient and physician denial impairs prompt appreciation of the gravity of prodromal cardiovascular symptoms, and because transport is often slow. To reduce transport delay, Pantridge,[6] in Belfast, has popularized mobile facilities staffed by physicians and equipped with monitoring and resuscitative devices. Although such units do reduce the risk of death during transport and reduce transport delay, unfortunately only approximately 12 patients have been resuscitated successfully each year by the Belfast group and only 22 of 15,000 with a similar program in Moscow.[1] Thus, it seems unlikely that mobile intensive care units by themselves will provide a definitive solution to the overall problem.

The efficacy of mobile units is limited by time. When primary ventricular fibrillation (that is, without previous ventricular failure) occurs in patients under observation in the cardiac catheterization laboratory or in the coronary care unit, correction of the dysrhythmia is the rule and the outcome is usually favorable. However, when definitive restoration of an endogenous rhythm is delayed even momentarily, a favorable outcome results much less often. Experience with mobile units indicates the extraordinary difficulty in reducing the unit response time from the onset of the episode to rescue crew arrival below 4 minutes.[2] In the study by Dr. Lewis and his associates, response time averaged 5.6 minutes from the receipt of alarm. The survival rate of patients with ventricular fibrillation was 10 out of 45, a figure probably indicative of unavoidable delay which limited potential salvage. The optimal attainable minimum elapsed time probably will not permit salvage rates approaching those achieved when primary ventricular fibrillation occurs in a controlled setting such as the hemodynamic or exercise laboratory or the coronary care unit.

Accordingly, one must consider other approaches of potential value in reducing mortality from sudden cardiovascular collapse in addition to implementation of effective mobile intensive care units. Possibilities include:

- Identification of populations at high risk suitable for prophylactic anti-arrhythmia drug administration.
- Precoronary care in special facilities available for self-referring patients attuned to the significance of prodromata.
- Utilization of electronic devices such as automatic self-contained catheter-defibrillation systems in selected patients at high risk.
- Aggressive surgical therapy designed to correct ischemia in selected patients before the onset of lethal dysrhythmia.
- Prevention of coronary artery disease with diet and other metabolic and pharmacologic interventions.

Many of these approaches depend on identification of criteria to define discrete, manageable populations of patients at particularly high risk. Since ventricular fibrillation appears to be responsible for most sudden death, premorbid electrocardiographic criteria have been sought. The instance of sudden death is 3 to 10-fold increased in patients with frequent ventricular premature beats, as was shown by Hinkle and coworkers[7] and in the Tecumseh study. Certain types of ventricular premature beats, such as those increased by exercise, those originating from the left ventricle, those falling during the vulnerable period, and those occurring in salvos appear particularly likely to precipitate sudden death. Unfortunately, however, precise selection of a population at high risk on the basis of ventricular premature beats is difficult because the phenomenon is so common, especially in older age groups. Perhaps, assessment of ventricular fibrillation thresholds in selected subjects will ultimately prove useful in this regard.

Risk factors such as hypertension, hyperlipidemia, diabetes mellitus, or previous overt coronary artery disease are present in most victims of sudden death. Unfortunately, populations at risk defined by such criteria are huge.

Most patients with acute myocardial infarction exhibit prodromata — usually chest pain — in the weeks preceding the acute episode. Even assuming that such prodromata generally precede sudden death as well, and that vigorous educational efforts succeed in encouraging patients to seek medical attention promptly, the difficulties of defining a manageable high risk population are formidable, if only because the symptoms are so common.

Thus, despite considerable progress, until more precise definition of risk is possible, widespread application of potentially hazardous prophylactic approaches to sudden death is not warranted. What has become clear is that a significant inroad on the overall mortality from sudden cardiovascular collapse and death will be possible only with a well integrated, multi-faceted program developed in part on the basis of ongoing research concerning risk factors; data processing and data reduction; instrumentation; patient and physician education; pharmacologic, metabolic, and surgical prophylaxis; as well as performance of paramedical personnel in mobile intensive care facilities.

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It Could Be an Historic Action

EARLIER THIS YEAR the American Medical Association and the American Nurses' Association created The National Joint Practice Commission (NJPC). This was done in response to a recommendation of the National Commission for the Study of Nursing and Nursing Education which strongly urged the establishment of joint practice commissions between medicine and nursing which would examine changing health care needs and functions and thus recommend improved practice roles for *both* medicine and nursing. The NJPC is now in the organizational phase at the national level and is actively encouraging the formation of state joint practice committees. One of them has been created in California.

One senses this action may well turn out to be of considerable historic significance, although it remains to be seen how much of a precedent has been set. However, two things appear to have been accomplished. The health team concept took a significant step forward when medicine and nursing agreed to establish a joint practice commission, and at the same time the nursing profession became recognized as a considerably more equal partner with the medical profession in patient care. Historic acts only become fully recognized in retrospect but they are apt to have historic consequences long before this recognition occurs. The historic consequences if any, of this joint action of the AMA and the ANA can at best be only dimly perceived at present.

But a look at the professed objectives and priorities of the NJPC may give some clue. These are understood to include (1) examination of roles and functions in medical and nursing practice with definition of new and altered patterns; (2) definition, identification and examination of health care needs; (3) improve communication between medicine and nursing to enhance joint planning and action; (4) propose changes in educational patterns and relationships that would enhance the new role functioning of nurses and physicians; (5) address the traditional problems which affect nurse-physician relationships in order to establish enhanced role functioning; (6) encourage and assist in the development of state counterpart joint practice committees; and (7) identify and address the ensuing problems related to the basic role reorganization.

There appears to be little that suggests preservation of the status quo in these announced objectives and priorities of the NJPC, and it seems quite likely that a new and no doubt powerful force has appeared upon the professional health care scene, one which quite clearly expects to bring about substantive rearrangements in the professional power structure at all levels of health care. Paradoxical as it may seem, this new alignment of medicine and nursing seems likely to presage both more coordination of patient care, which is desirable, and at the same time more fractionation among the health professions, which may or may not be so desirable. In any case a precedent seems to have been established, and the way therefore opened for other professionals on the health care team to become increasingly recognized as actively participating partners in decision-making for medical and health care.

The primary concern of all should of course be the welfare of the patient, and it remains to be seen whether or to what extent the patient will benefit. It would seem likely that to the degree better coordination of patient care is achieved, the patient will indeed benefit, and to the degree that fractionation and divisions among a gaggle of health professions dominate the scene, the patient will inevitably suffer. We hope that the forces for cohesion will outweigh the forces for division, but suspect that to bring this off will take a bit of doing, particularly by physicians, who must clarify the role of the medical profession as new arrangements with other professions in patient care inevitably evolve.

—MSMW

Proposition 2

For Health Sciences Facilities

On November 7, California voters will have an opportunity to take action at the polls which will directly alleviate the health manpower shortage in the state. By voting for Proposition 2 for Health Sciences Facilities, they will make it possible for the state to increase by 73 percent the number of health professionals educated each year.

Proposition 2 will provide through the sale of state bonds $155.9 million to the University of California for construction and expansion of health sciences facilities on seven of its nine campuses. This will allow the state of California to train more physicians, dentists, nurses, optometrists, pharmacists, public health specialists, and veterinarians. The cost to the average taxpayer will be about 50 cents a year for a maximum of 30 years, or a total of about $15. The bonds will be paid off from taxes paid on income, cigarettes, ale beverages, corporations, gifts and horse racing, and not from property taxes.

Only a simple majority, or a 50.1 percent "yes" vote, is required to pass Proposition 2.

Expansion of the health sciences facilities will allow the enrollments in the University's health sciences programs to grow from the present 7,015 to 12,171 annually. Passage of the bond measure will increase the annual enrollments in medicine by 79 percent, dentistry by 52 percent, nursing by 31 percent, optometry by 73 percent, pharmacy by 43 percent, public and community health by 93 percent, and veterinary medicine by 69 percent. In addition, it will allow the University to train a new category of health worker, physician's assistants, in developing programs. Enrollments are tentatively estimated to total 250 over the next five years.

Unless Proposition 2 is passed, there appears to be no possibility that the health sciences schools in the University of California can significantly expand their output. In fact, if Proposition 2 fails there is every likelihood that the current level of health workers trained in the University of California will decrease, particularly in the fields of dentistry and optometry.

Voter approval of Proposition 2 will also make the University of California eligible for about $100 million in matching federal construction funds. None of the money could be used for any purpose except construction of health sciences facilities. The $155.9 million provided by the sale of state bonds would be available as needed for annual appropriation to the University under the regular state budgetary procedures whereby all projects are subject to detailed review and approval by the Governor and the Legislature.

The health sciences facilities bond measure, Proposition 2, was approved for the November 7 ballot by the Legislature with only one dissenting vote. It has received the endorsement of Governor Ronald Reagan, former Governor Edmund G. "Pat" Brown, the California Medical Association, the California Hospital Association, the California Dental Society, the California Optometric Association, the California Veterinary Medicine Association, the California State Chamber of Commerce, the California Labor Federation, the Mexican-American Labor Council and many others.

The projects which would be funded by passage of Proposition 2, and the projected total enrollments in the University's health sciences schools by campus are:

Berkeley—addition to the Optometry Building to expand clinical teaching facilities, and a Health Sciences Building to expand the School of Public Health; optometry enrollment, 343; public health, 415.

Davis—Medical Sciences Unit 1 for basic sciences and a health science library, Medical Sciences Unit 2 for an on-campus clinical teaching facility, alterations in clinical teaching facilities in affiliated hospitals, and Veterinary Medicine Unit 2 for basic and clinical sciences expansion in the School of Veterinary Medicine; medical enrollment projected at 1,210; veterinary enrollment, 738.

Irvine—Medical Sciences Unit 1 for basic sciences and a health sciences library, and Medical Sciences Unit 2 for an on-campus clinical teaching facility; medical enrollment projected at 1,156.

Los Angeles—completion of unfinished space in the School of Dentistry Building to improve teaching support facilities, alterations for the School of Medicine for improving existing facilities, removal of safety deficiencies in the Health Sciences Center, and a School of Nursing Building to relocate and expand the School; projected dentistry enrollment, 501; medical enrollment, 1,973; nursing enrollment, 330.

Riverside—Basic Sciences facilities; enrollment projected at 40 students (students in the first two years of the MD curriculum who will transfer to UCLA to complete their clinical training).

San Diego—purchase of equipment for Clinical Sciences Building and improvements and additions to University Hospital of San Diego County to expand clinical teaching facilities; medical enrollment projected at 1,145.

San Francisco—a dentistry building to expand the School of Dentistry, Medical Sciences and UC Hospital alterations primarily for the School of Medicine but also for the School of Human Biology and the School of Pharmacy, Moffitt Hospital alterations; projected dentistry enrollment, 652; human biology, 250; pharmacy, 572.

CASE REPORTS

Refer to: Fauvre FM, John DR, Watkins LE: Cardiomyopathy secondary to pheochromocytoma. Calif Med 117:58-60, Oct 1972

Cardiomyopathy Secondary To Pheochromocytoma

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MYOCARDITIS HAS BEEN PRODUCED experimentally by catecholamines since adrenalin was first synthesized in 1904, initial experiments having been done by Ziegler in 1905[1] and Pearce in 1906.[2] Not until Szakacs and Cannon[3] did so in 1958 had anyone described a specific focal myocarditis, indistinguishable from that produced by norepinephrine infusions, in association with human pheochromocytoma. Since then, there have been additional articles[4,5,6] reporting a total of 24 cases of myocarditis associated with pheochromocytoma.

The following is a report of a case of progressive, terminal myocarditis which at autopsy proved to be due to pheochromocytoma.

Report of a Case

The patient was a 47-year-old Caucasian man, who first became symptomatic in late November, 1970. He noticed gradual onset of dyspnea on exertion, and later hemoptysis. In December he was admitted at another hospital and transferred to Riverside General Hospital after three days. Pertinent medical history was of hypertension, treated with sodium butabarbital and reserpine (Butiserpine®) from 1963 until 1966 at which time he had been told he no longer needed medication. He said that he had had night sweats intermittently over several months before admission and he spoke of himself as a "nervous" person.

On initial admission, blood pressure, sitting, was 180/130 mm in both arms but was normal when taken subsequently and throughout most of his hospital stay. He was observed to be thin, in moderate respiratory distress, sweating mildly and quite anxious-appearing. The pulse rate was 112, with a prominent S_3 gallop. On examination of the lungs, decreased breath sounds and dullness to percussion posteriorly were noted. The liver was palpable 6 cm below the right costal margin, there was no ascites and no evidence of peripheral edema. An x-ray film of the chest

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Submitted December 23, 1971.

Reprint requests to: F. M. Fauvre, M.D., 5634 Malvern Way, Riverside, Ca. 93506.

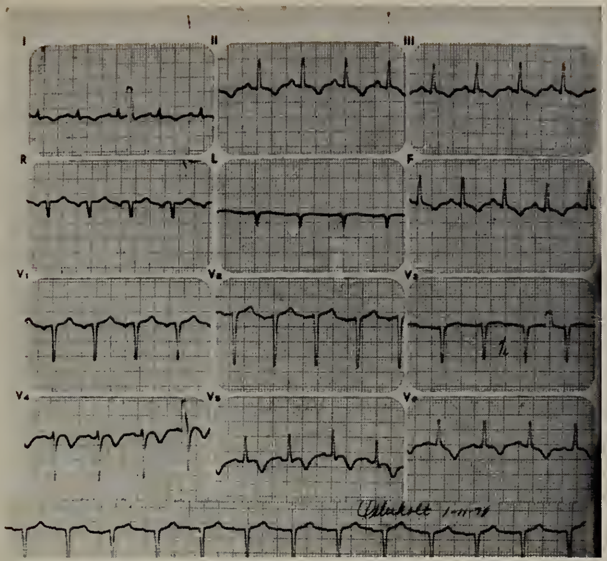

Figure 1.—**EKG taken during first hospitalization, showing T wave inversion consistent with myocarditis.**

showed bilateral pleural effusion, and thoracentesis on admission produced 1200 ml of fluid from each chest cavity. An electrocardiogram showed T wave inversion consistent with myocarditis (Figure 1). Cope needle biopsy of the pleura revealed chronic inflammation.

The patient was treated with digitalis and diuretics and bed rest on the chest ward for one month and his condition improved dramatically. Studies done at that time ruled out granulomatous disease.

The patient was discharged with the diagnosis of viral myocarditis, and regular visits to the cardiac clinic were scheduled. Limited activity at home was prescribed, but he did poorly at home, requiring frequent trips to the emergency room, and he was readmitted 27 May 1971 with progressive congestive failure. The patient responded dramatically to intravenous furosemide, and the next day was transferred to the ward. That night his temperature rose to 40.6°C (105°F), and he had hemoptysis, dyspnea and anxiety. No sources of possible embolic phenomena were evident on physical examination. He was treated with heparin, and morphine and oxygen also were given. Fluid withdrawn at thoracentesis done on admission was sterile; a sputum culture grew Staphylococcus aureus, coagulase positive, and cephalothin sodium (Keflin®) was given intravenously.

A lung scan showed a larger perfusion defect than the lesion on chest x-ray which was consistent with pulmonary embolus. The patient's condition deteriorated progressively until he died, 12 days later. During the last 48 hours he received dexamethasone, 8 mg by intravenous bolus followed by 4 mg intravenously every four hours for four doses. This was discontinued when guiac-positive material and a small amount of blood was aspirated from a nasogastric tube. The patient became progressively more lethargic and died June 6. At autopsy a 70-gram pheochromocytoma of the right adrenal and a large hemorrhagic area in the interventricular septum of the heart were observed (Figure 2). Multiple pulmonary emboli, source undetermined, and superficial ulceration of the stomach were also found. Sections from the hemorrhagic area in the interventricular septum of the heart showed extensive muscle necrosis without acute inflammatory response (Figure 3). There were areas where the muscle cells appeared to have ruptured, and be-

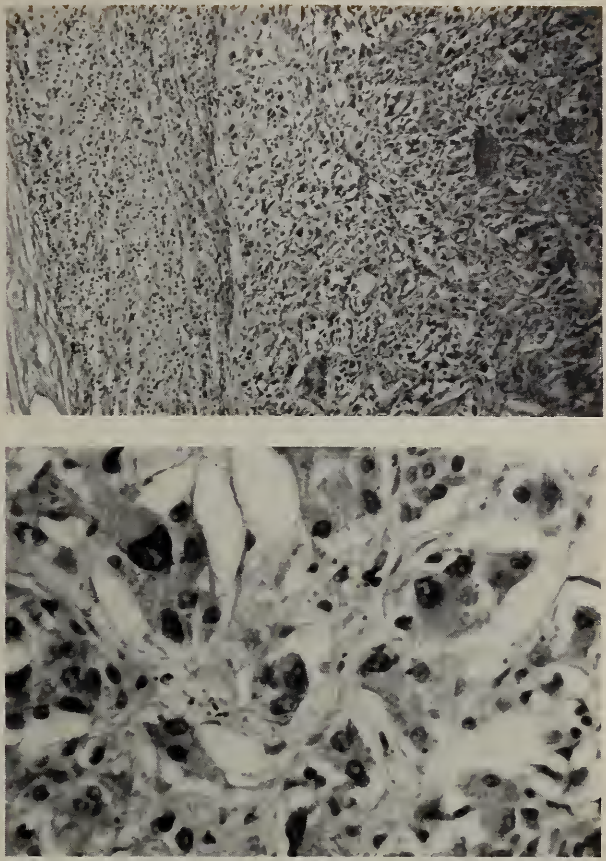

Figure 2.—***Upper,*** **low power view of pheochromocytoma showing the tumor on the right, and a thin layer of adrenal cortex covered by connective tissue on the left. The higher power view below shows large cells with abundant granular cytoplasm characteristic of adrenal medulla.**

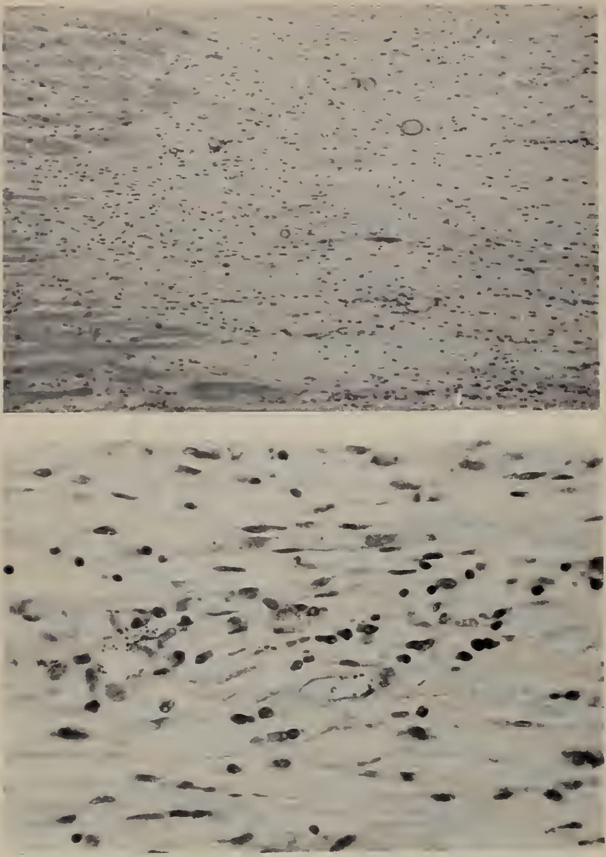

Figure 3.—Low and high power magnification of involved heart muscles, showing infiltration with chronic inflammatory cells, myocytolysis and scarring, characteristic of catecholamine myocarditis.

tween these cells was an amorphous blue-staining material. These changes were thought to be consistent with "myofibrillar degeneration."[7] In addition to the foci of necrosis and recent hemorrhage there were areas showing replacement of muscle fibers by loose connective tissue containing a few mononuclear inflammatory cells. These areas did not show the dense collagenous scar tissue typical of old myocardial infarcts, but were more typical of "myocytolysis."[8] Myocytolysis is thought to be a late stage of "myofibrillar degeneration" and both lesions are described in patients who die with pheochromocytoma.[4,7]

Discussion

Myocarditis was found in 58 percent of 26 patients with pheochromocytoma in a retrospective study by Van Vleit in 1966.[6] The histologic changes have been well characterized[7] and identical lesions have been produced experimentally by injections of catecholamines.[6] The diagnosis of pheochromocytoma can be made on the basis of urinary catecholamines and their metabolites even in the patient with congestive failure and diaphoresis,[9] but to date the majority of the reported pheochromocytomas have been diagnosed at autopsy.[10] Experiments with dog heart-lung preparations have shown that corticosteroids augment the cardiac muscle toxicity of catecholamines.[11,12] In the case here reported the patient received a short course of dexamethasone, which may have had a synergistic effect with the endogenous sympathomimetic hormone against his myocardium.

Pheochromocytoma should be considered in the differential diagnosis of myocarditis.

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Refer to: Sokol AB, Adler L, Morgenstern L: The synchronous association of villous adenoma with colonic adenocarcinoma. Calif Med 117:61-64, Oct 1972

The Synchronous Association Of Villous Adenoma with Colonic Adenocarcinoma

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THE MULTICENTRICITY OF NEOPLASTIC growths has been frequently reported in the recent literature.[1,3,7,11] A relationship of villous adenomata occurring synchronously with other neoplasms, although noted, has not been the subject of a report.[2,5,6,8,12] Three cases are presented here along with a summary of the incidence of these synchronous lesions as determined from the literature.

Case Reports

Case 1. A 65-year-old white man was admitted with a large bowel obstruction secondary to carcinoma of the sigmoid. After decompression transverse colostomy the patient was returned to surgery where an annular carcinoma of the sigmoid was seen to extend transmurally and invade a contiguous loop of sigmoid, producing a closed loop obstruction (Figure 1). Micropathologic study revealed typical adenocarcinoma (Figure 2). Abdomino-perineal resection with left colectomy and resection of a synchronous villous adenoma of the rectum was carried out. In the fixed state (Figure 3) the typical villous projection of the tumor and its near circumferential involvement of the rectal wall was apparent, and microscopically it was of villous pattern (Figure 4).

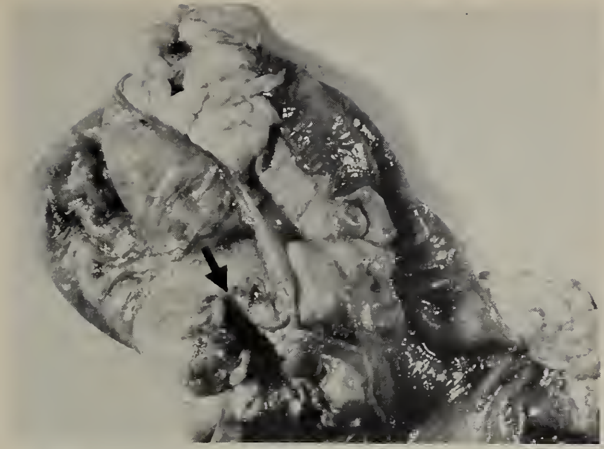

Figure 1—An ulcerating adenocarcinoma of the distal sigmoid colon (arrow). The tumor penetrated all layers and involved the contiguous proximal sigmoid loop which led to the closed loop obstruction.

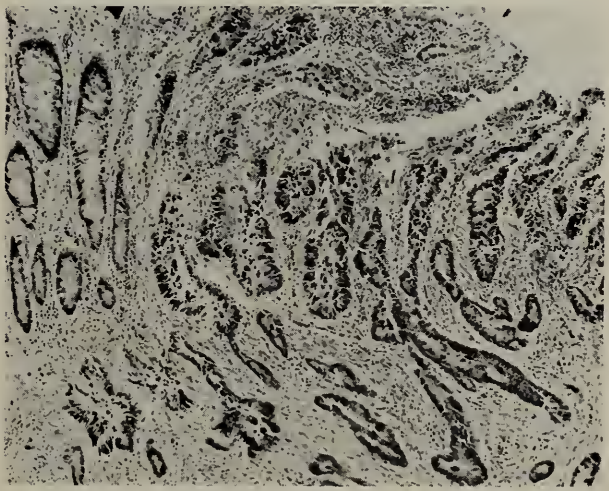

Figure 2—Microscopic view (X50) of Figure 1 shows representative field of a typical poorly differentiated adenocarcinoma of the sigmoid colon.

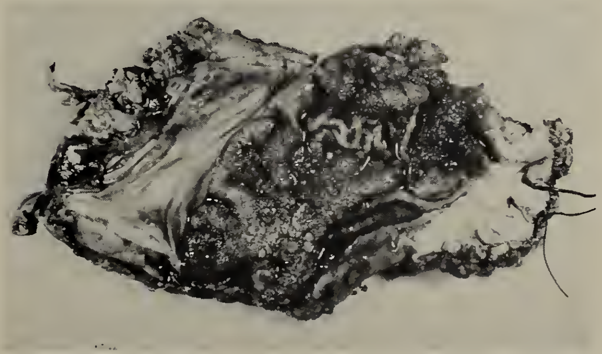

Figure 3—Formalin fixed anorectal segment of abdomino-perineal resection. A typical villous adenoma with papillary features is seen involving almost the entire circumference of the rectum (suture attached to anal verge).

From Cedars-Sinai Medical Center, Cedars of Lebanon Hospital Division, Los Angeles.

Submitted October 18, 1971.

Reprint requests to: L. Morgenstern, M.D., Director of Surgery, Cedars of Lebanon Hospital, 4833 Fountain Avenue, Los Angeles, Ca. 90029.

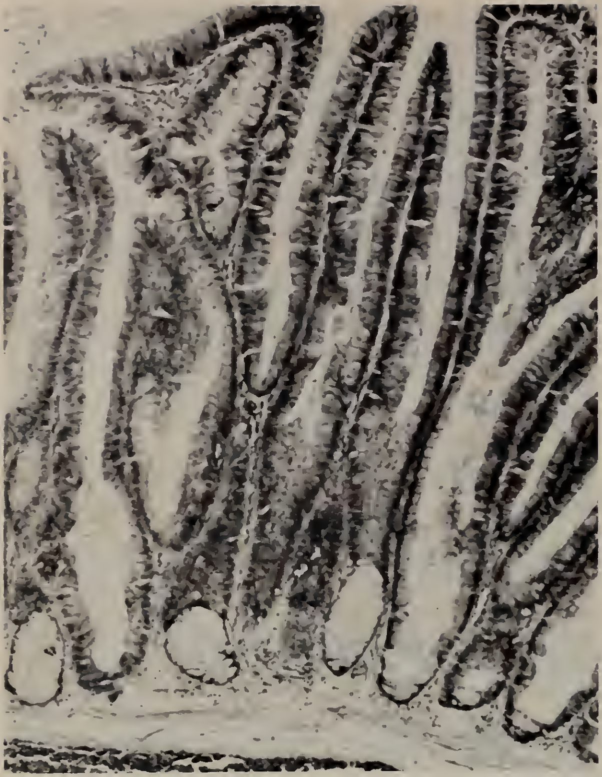

Figure 4—Microscopic (X50) picture of the rectal villous adenoma in Figure 3. Characteristic villous processes with moderate cellular atypism and nuclear stratification are clearly seen.

Case 2. A 64-year-old white man was admitted with a large bowel obstruction secondary to an annular carcinoma of the descending colon seen roentgenographically in barium enema studies. Proctoscopic examination and barium study (Figure 5) confirmed the finding of a synchronous villous adenoma of rectum, measuring 9 x 4 cm and situated on left anterolateral wall 5 cm proximal to the anal verge. A decompression transverse colostomy was performed and five weeks later the patient was returned to surgery for a left colectomy. The carcinoma grossly was an annular lesion and microscopically was a typical adenocarcinoma (Figure 6). Two months later the patient was returned to surgery where, through a posterior rectotomy, the villous adenoma of the rectum was excised (Figure 7). The typical gross villous feature of the tumor—a velvety, papillary surface—may be seen in Figure 8. Six months later closure of the transverse colostomy was carried out.

Case 3. A 68-year-old white woman complained only of weight loss and on sigmoidoscopy was found to have a villous adenoma about 7.5 cm proximal to the anal verge, measuring 4 x 4 cm and situated on the right anterior wall. Biopsy confirmed the diagnosis (Figure 9). In addition, a barium enema study disclosed an an-

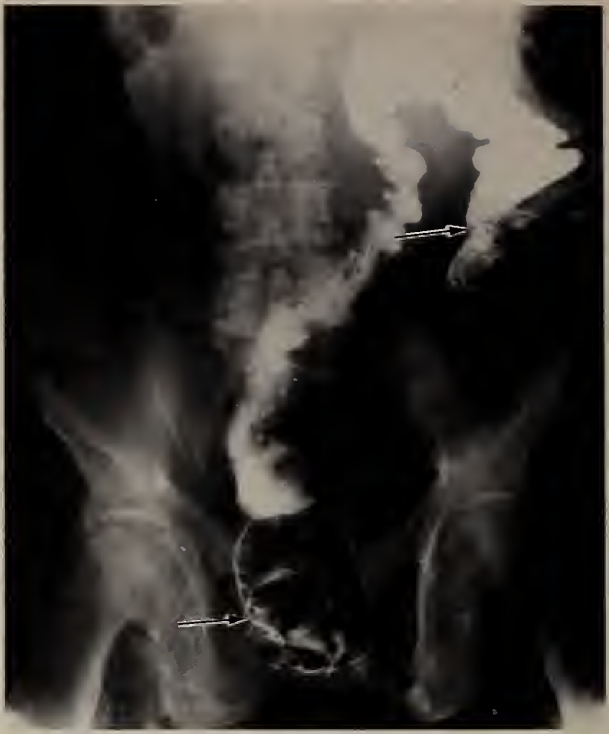

Figure 5—Selected view of barium enema series demonstrating obstructing annular carcinoma of descending colon (top arrow). An air contrast study of the rectal ampulla demonstrates the villous adenoma (bottom arrow).

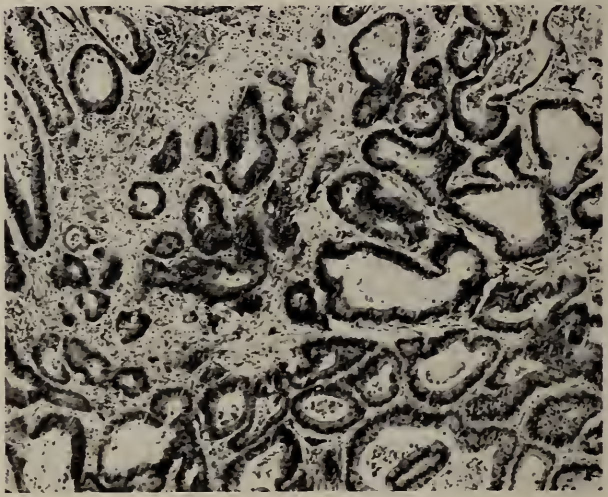

Figure 6—Microscopic view (X50) demonstrating a well differentiated carcinoma of the descending colon.

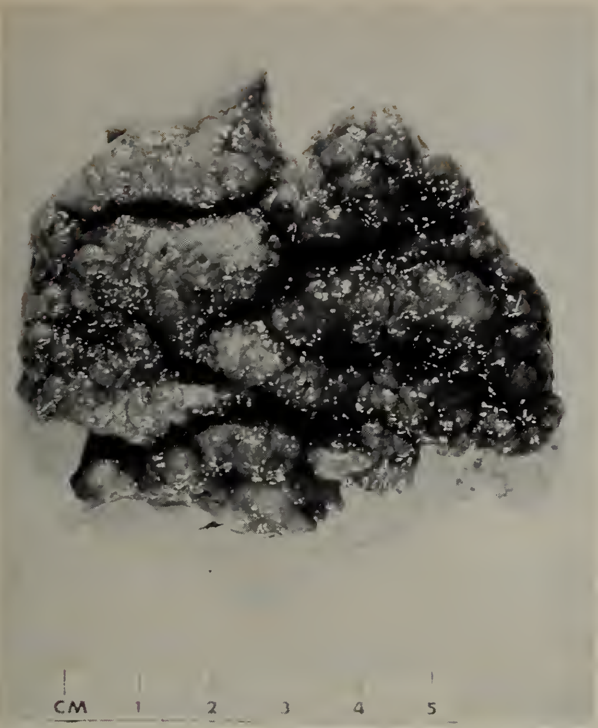

Figure 7—Gross appearance of resected villous adenoma of the rectum. Not the typical velvety, papillary appearance.

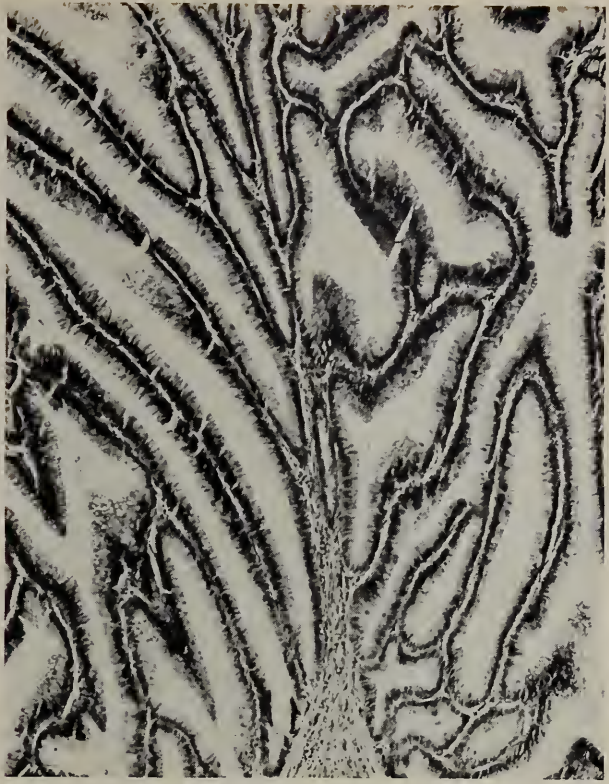

Figure 8—Microscopic (X50) picture of villous adenoma shown in Figure 7. Note the characteristic fronds or villous pattern with only minimal cellular atypism.

nular lesion of the proximal sigmoid colon. At operation metastasis to the liver was observed and a palliative sigmoid resection was carried out. Figure 10 shows the microscopic pattern of an infiltrating well differentiated adenocarcinoma.

The patient did relatively well postoperatively and received chemotherapy. The villous adenoma was treated by combined local excision and fulguration.

Discussion

Several interesting associations have been noted recently with villous adenomas; two have received much attention in recent years. First is the fascinating fluid and electrolyte deficiency syndrome, associated with the mucorrhea of these neoplasms.[4,10] The second is the 25 to 35 percent incidence of malignant degeneration occurring within these benign lesions.[6,8,9] A third aspect and the subject of this paper is the synchronous association of benign villous adenoma with colonic adenocarcinoma.

That there may be multiple lesions of the colon is, of course, well known. Adenomatous polyps occur in 10 percent of the cases of colonic adenocarcinoma[8] and the adenocarcinomas are multiple in about 5 percent of cases.[1,3,4] This incidence rises to 12 percent when focal carcinoma-in-situ occurring in adenomatous polyps is considered.[1]

Taking only villous adenoma in consideration, Nicoloff reported that up to 57.5 percent will be associated with polyps of the colon.[5] The actual association of villous adenoma with synchronously occurring colonic adenocarcinoma is anywhere from 5 to 7.2 percent.[2,5,6,7,8,9]

Certain clinical features of the synchronous association of colonic adenocarcinoma and villous adenoma should be pointed out. Two of the patients in the cases presented herein had manifestations of large bowel obstruction secondary to the proximal obstructing carcinoma, but there are no unique symptoms or signs of these associated lesions. An exception is the synchronous villous adenoma producing mucorrhea with or without profound symptoms of fluid and electrolyte deficiency.

The villous adenoma is in the rectal area in more than 90 percent of cases,[8] and the diagnosis

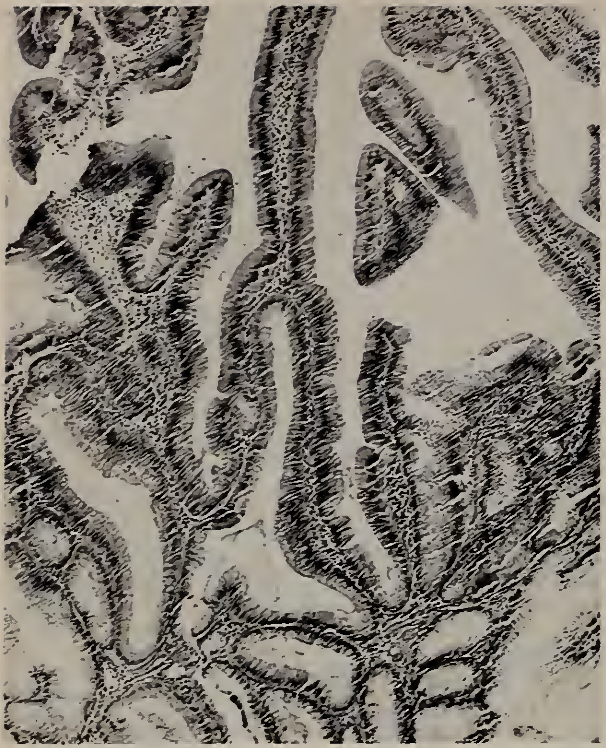

Figure 9—Biopsy specimen of the rectal villous adenoma with typical papillary features and minimal cellular atypism (X85).

is usually made by the sigmoidoscopic examination, as the gloved finger cannot easily distinguish the soft frondlike pattern of the adenoma from the adjacent mucosa. There are a significant number of villous adenomata occurring above the peritoneal reflection as far proximal as the cecum. The site of the adenoma may therefore be proximal or distal to the colonic adenocarcinoma.

Although attention may first be directed toward surgical extirpation of the adenocarcinoma, multiple biopsy specimens of the adenoma should be studied to rule out malignant degeneration. If malignant, the villous lesion should be excised simultaneously with the adenocarcinoma, if possible, or soon after. Finally, the electrolyte and fluid deficiency syndromes, although not often occurring, may be so profound as to necessitate surgical extirpation of the benign villous adenoma before or perhaps concomitantly with removal of the colon cancer.

Conclusion

Observation of a villous adenoma or of any colonic neoplasm for that matter, should stimulate a search for other colonic lesions. Similarly, postoperative examinations if performed routinely can be expected to discover a metachronous carcinoma, that is a second primary malignant lesion, in at least 5 percent of the cases[1] and a benign polyp in at least 10 percent.[8]

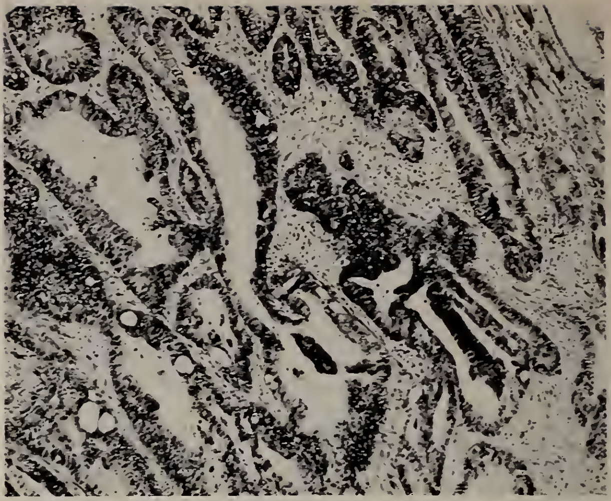

Figure 10—Microscopic appearance of a fairly well differentiated adenocarcinoma of the sigmoid colon (X85).

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Refer to: Parker CE, Mavalwala J, Koch R, et al: Syndrome associated with the partial deletion of the long arms of chromosome 18 (18q–). Calif Med 117:65-71, Oct 1972

The Syndrome Associated With the Partial Deletion Of the Long Arms of Chromosome 18 (18q–)

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The syndrome associated with the partial deletion of the long arms of chromosome 18 (18q–) is now well accepted by geneticists. This subtle syndrome can be suspected by an alert clinician, but the diagnosis cannot be made without the aid of a chromosomal analysis. Mental retardation, hypotonia, short stature, atretic or stenotic auditory canals, abnormal hearing, midface dysplasia, and spindle-shaped fingers with an unusual number of whorls on the fingers should suggest the syndrome. This paper describes two children with an 18q– deletion and discusses the salient features of the syndrome.

Reports of Cases

Case 1. The patient, a girl four years and four months old when first seen, was born to a 33-year-old para IV, gravida IV mother and 36-year-old father. The pregnancy was uneventful and the gestation period was nine months. Labor lasted four hours and resulted in a normal vaginal delivery.

The child weighed 6 pounds 8 ounces, was 20 inches long and had a head circumference of 13½ inches. Her cry was spontaneous and she appeared normal at birth. She was discharged from the nursery on the third day of life.

She smiled at one month, sat without support at eight months, stood at ten months and walked alone at 18 months. She could say "mama and dada" at eight months but had no other words until she was approximately two years old.

The parents first became concerned when she was about two and a half years of age because of delayed development as compared with her siblings. At this time the child was seen by an orthopedist because of tibial torsion and bilateral pronation of the feet.

The child presented at age four years and four months as a slender Mexican-American girl with a flat face. She comprehended simple instructions and had a vocabulary of approximately 25 words. Her voice was harsh and raspy and she occasionally had outbursts of crying. She was 39 inches tall, weighed 28 pounds, had an arm span of 38 inches and her sitting height was 22 inches. Her vital signs were normal.

Her head was normocephalic with a head circumference of 18¾ inches. The hair was fine, black and occasionally sparse over the skull (Figure 1). The conjunctivae, pupils and fundi were normal. The ears were low set with thin helices and prominent antihelices (Figure 1). The external canals and tympanic membranes appeared to be normal and the hearing was grossly normal. The nose was broad, flat and somewhat concave (Figure 1). The palate was high and arched and the mouth turned down but the teeth were normal. Examination of the chest and heart was normal. There was a small umbilical hernia and normal genitalia. The neurological examination revealed generalized hypotonic reflexes in all extremities with good muscle tone and Babinski's sign not present. The patient had incurved fifth fingers and spindle-shaped fingers bilaterally.

The family history was non-contributory. The proband had no younger siblings. There was a 17-year-old half-brother, a 12-year-old half-sister and a five-year-old brother, all said to be normal.

Case No. 2. The patient, a 16-year-old boy, was born by cesarean section, weighing 4 pounds

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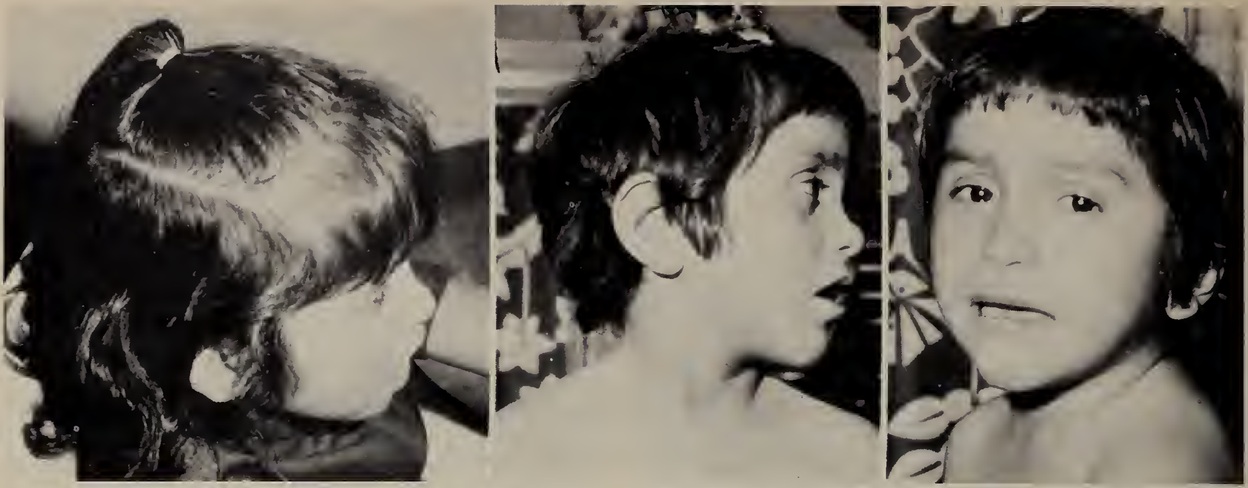

Figure 1.—Frame at left shows sparseness of hair (Case 1). *Center,* note the shape and position of the low-set ear. Mid-facial dysplasia is also present. *Right,* the general shape of the face. The mouth is fish-like, the mandible prominent.

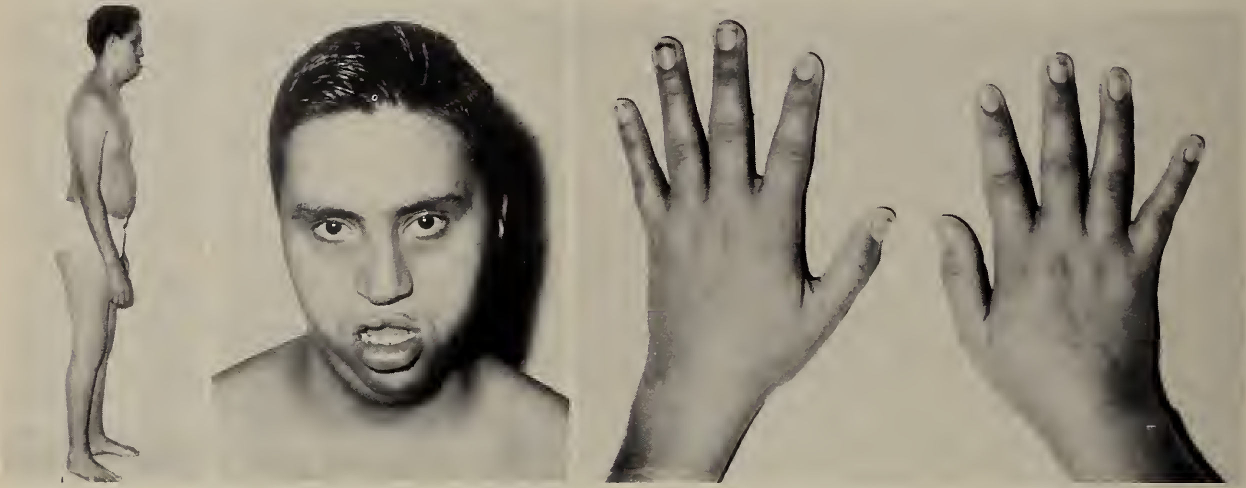

Figure 2.—*Left,* the general habitus of the patient in Case 2. The mid-facial dysplasia and prominent mandible is evident. The abdomen is slightly protuberant. *Center,* facial characteristics. *Right,* the slight tapering of the fingers is characteristic of the syndrome.

3 ounces, to a para IX gravida X mother who had diabetes mellitus and was ill during most of the pregnancy. The mother was 34 years old and the father was 37. The child was born with a unilateral cleft lip and palate which was repaired when he was 10 months old. At the age of 11 months the child was admitted to hospital with pneumonia. At this time the hemoglobin was 7.5 grams per 100 ml.

The child passed his developmental milestones slowly and by the age of three years he had begun to have "fainting" spells. By the age of five years the child had been labeled "Down's syndrome with mental retardation, epilepsy and right hemiplegia." He has been in a special school and functions in the range of a 50 IQ.

At age 16 years 7 months the boy presented as a short, shy, cooperative Mexican-American who was alert and aware of his surroundings. He could walk, feed himself and take care of all his personal needs. His speech was poor and he was difficult to understand. His posture was poor. He was 56½ inches tall, weighed 132 pounds and his head circumference was 22½ inches.

There was pronounced mid-facial dysplasia, giving the head the appearance of having decreased anterior-posterior diameter (Figure 2). The hair was fine and black and was sparse over

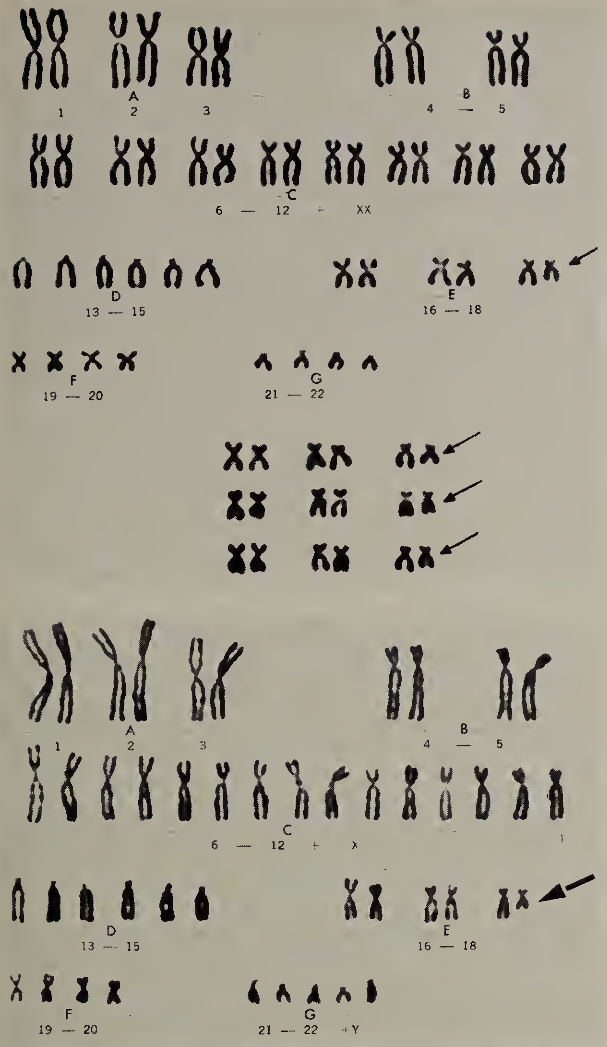

Figure 3.—The standard karyotypes of the two patients (Case 1 above and Case 2 below). Each has 46 chromosomes. The arrows indicate the partial deletion of the long arm of chromosome No. 18.

the temple. The eyes did not appear wide-spaced and the fundiscopic examination was normal. The ears were low-set with thin helices and the antihelices prominent. The external canals and tympanic membranes were normal and the hearing was normal. The nasal bridge was broad. The upper lip was scarred secondary to the cleft repair (Figure 2). The palate was high arched and uneven. The teeth had erupted in an irregular manner. The chest and heart were normal. The abdomen was protuberant (Figure 2) but there were no masses or organomegaly. The testes were present in the scrotum, measured approximately 3.2 cm in length and had normal texture. The reflexes were hypotonic throughout. The fingers were spindle-shaped (Figure 2).

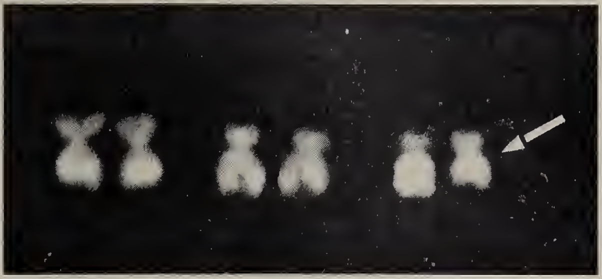

Figure 4.—The partial karyotype of the E group chromosomes of the patient in Case 1, using the new quinocrine hydrochloride fluoromicroscopic technique. The differential banding of the E group chromosome is clearly discernible making positive identification easy. The arrow indicates the chromosome with the deletion.

The mother died of diabetes mellitus and infection at age 44. The father is 51 and in good health. The proband is the tenth of the ten children. All the siblings are said to be normal.

Laboratory Data

In both cases the electroencephalograms were normal as was the urine amino acid chromatography. Serum protein electrophoresis and the quantitative immunoglobulins were normal, including IgA. The karyotypes (Figure 3) showed partial deletion of the long arm of chromosome 18. Figure 4 shows a partial karyotype of the E group, using the quinacrine hydrochloride fluoromicroscopic technique. The karyotypes of the living parents were normal.

The finger dermatoglyphics of the patient in Case 1 (Figure 5) showed a clear excess of composite patterns. Her total ridge count was 167. The finger patterns of the other patient (Figure 6) were also complex. His total ridge count was 134.

Discussion

The partial deletion of the long arms of chromosome 18 was first reported by deGrouchy et al[1] in 1964 and a formalization of the phenotypic aspects of the syndrome was presented by Lejeune[2] et al in 1966. Table 1 summarized the major physical findings of the syndrome. Not all patients show all the malformation, which probably reflects the amount of chromosomal material deleted. Lejeune (1966)[2] suggested that the malformations present in patients with an 18q− defect were the antithesis of those observed in the 18 trisomy syndrome. However,

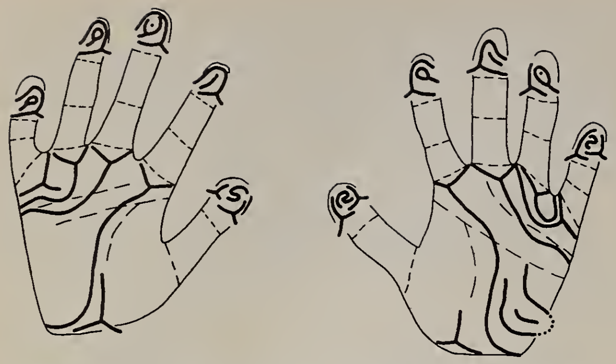

Figure 5.—The complex patterns of the fingers are demonstrated in this figure. These patterns, like whorls possess two triradii, but are unlike whorls formed by the combination of two loops twisted into one another. The patient in Case 1 in fact possesses no whorls at all. She has eight patterns, and two simple loops opening in the ulnar direction. Of the eight patterns five are center pocket loops, two are lateral pocket loops, and one is a twin loop. Her total ridge count of 167 is high. On the right palm a transitional form of a single transverse flexion crease can be observed. The proximal transverse flexion crease traverses the entire width of the palm. Main line D of the left palm is abortive. This is a rare feature.

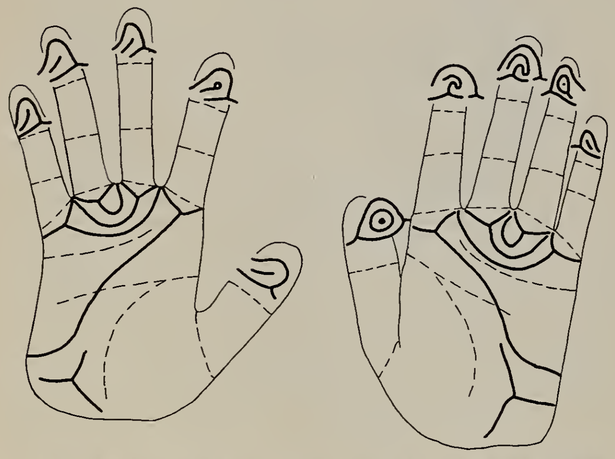

Figure 6.—There are five complex patterns (Case 2) of which one is a true whorl and the other four are composite patterns. The patient also has five ulnar loops. His total ridge count is 134. There is a transverse main line D and a longitudinal main line A.

as Wertelecki et al[3] have pointed out, the same organ is commonly malformed in both syndromes but the nature of the malformation is neither antithetical nor identical.

All patients reported, with the exception of a case reported by Wertelecki and Gerald[4] have been mentally retarded. Their patient, however, showed an unusual cytogenetic lesion in that 28 of the 37 cells examined showed the deletion of the long arm of chromosome 18 and in the remaining 9 cells a ring chromosome 18 was present.

The most prominent physical abnormalities have involved stature, ears, eyes, face, heart, dermatoglyphics and genitalia.[5] Fischer[6] pointed out that her patients showed areas of sparse hair growth, as did the patient in Case 1.

Identification of the E group chromosomes has been made simpler with the appearance of quinacrine fluormicroscopy. This technique reveals characteristic and reproducible patterns in all human mitotic chromosomes. It is valuable not only in identifying similar pairs (Figure 3c) but is also an enormous aid in identifying gross structural rearrangements.

Immunoglobulin

In 1968 Feingold et al[8,9,10] reported the immunoglobulin IgA to be missing in two patients. They studied one with a ring chromosome 18 and the other with deletion of the long arm of chromosome 18. These findings suggested that a locus controlling the synthesis of IgA was on the deleted segment of the chromosome. Since that time, some investigators have confirmed this observation[11] while others have reported normal or elevated levels of IgA in their patients.[12]

The IgA system is thought to play a major role in the mechanism of resistance to upper respiratory infection.[13] It is known to be the predominant immunoglobulin in saliva, tears, and nasal secretions. Abnormality of this immunoglobulin has been found in malabsorption syndromes,[15] ataxia telangiectasia,[16] autoimmune diseases[17] and it has even been reported in healthy persons.[10]

Several investigators have reported an increase in upper respiratory infections in their patients with the 18q– syndrome[5,9] while others with patients having an IgA deficiency have reported no such symptoms.[18] Our patients had normal levels of IgA and did not have a history of frequent infections.

This apparent discrepancy could be explained by a state of mosaicism whereby the patient possesses two cell lines, one abnormal and the other normal. A small proportion of normal cells would be sufficient to produce the IgA. Secondly, since interpretation of the deletion is gross, it is impossible to tell exactly how much of the arm

TABLE 1.—*Summary of the major physical defects that have been reported with the 18q– syndrome, and the findings in two cases*

Summary of the Most Important Defects Reported in 18q– Syndrome	*Summary of Defects Found in Patients Reported*	
	Patient #1	*Patient #2*
1. Mental retardation	Yes	Yes
2. Short stature	Yes	Yes
3. Microcephaly	Borderline	No
4. Midface dysplasia	Yes	Yes
5. Impaired hearing with hypoplastic or atretic canals	Hearing normal Prominent antihelix	Hearing normal Prominent antihelix
6. Carp-shaped mouth	Yes	Borderline
7. Fusiform fingers with an increase in the number of complex patterns	Yes	Yes
8. Dimples of the epitrochlea, sides of the kneecaps and backs of the hands	No	No
9. Hypotonia	Yes	Yes
10. Ophthalmologic anomalies	No	No
11. Genital anomalies	No	No
12. Congenital heart disease (asymptomatic)	No	No
	In addition our patients exhibited areas of sparse hair over the temples.	

is deleted. It is possible that in some instance the IgA locus remains on the intact portion of the long arm thereby providing normal levels of IgA in a patient with the 18q– syndrome. Thirdly, one must also consider the possibility that the effect of the chromosomal deletion on IgA may be nonspecific. Obviously, more cases of this syndrome need to be recognized and studied and conversely in those patients in whom IgA is found to be absent, a karyotype should be performed.

Dermatoglyphics

Referring to Figures 7 and 8 the reader will find a general summary and explanation of the nomenclature of dermatoglyphics. It is now established that the dermatoglyphics of patients with the 18q– syndrome[1,3,5,19-26] are affected.

The published data have so far reported on the fingers and palms, and only on the hallucal area of the sole. No toe print data is available.

On the fingers, the dermal patterns are increased in geometric complexity. An increase in gross size is also observed and is clearly reflected by an increased ridge count.

The complex patterns observed on the fingers of these patients are erroneously reported as whorls. It should be noted that dermal finger patterns vary in a continuous series from simple configurations such as arches, to very complex configurations.

In those 18q– patients whose prints we have been able to observe directly, the patterns are complex in a specific direction. The patterns are not all true whorls. They are composite patterns of the multiple loop variety. The patterns are also vertically extended to the extent that the proximal edge of the pattern lies below the flexion crease of the finger-ball. The large size also moves the lateral margins of the pattern beyond the area of the ridged skin resulting in extra-limital triradii. While the marginal areas of the patterns are thus distended, the core area is clearly vertically distended.

What is significant here is that not only do 18q– patients possess complex finger patterns in clear excess of what is expected when comparisons are made with their parents and siblings,[26] but that these cannot be counted as merely an increase in whorls. The patterns are an increase in composites and these are then large and vertically oriented. This vertical orientation is particularly seen in the core area.

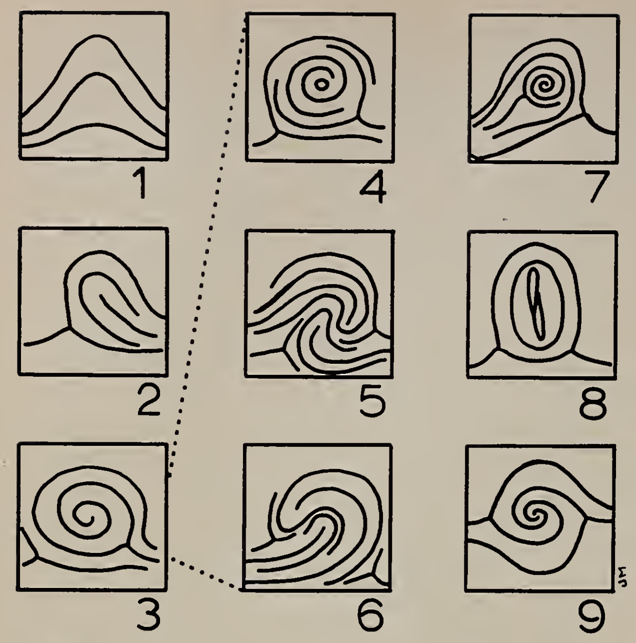

Figure 7.—

1. *Arch,* formed by the ridges flowing across the ball of the finger in the form of a wave. No triradius is observed. If a triradius is seen at the base of the wave the pattern is referred to as a *tented arch.*
2. *Loop,* formed by recurving ridges opening laterally, either in the ulnar or radial direction. One triradius. The number of ridges that touch a line projected from the triradius to the central *core* line of the pattern constitutes the ridge count.
3. *Whorl,* formed by concentric skin ridges or spiralling ridges resulting in a circular or elliptical pattern bounded by two triradii. Two ridge counts, one from each triradius to the core, are made. The higher of the two is used to calculate the total ridge count, which is the sum of the figures from all ten fingers.

Type three can better be considered the sum of the next six types. What are ordinarily reported as whorls would only be Types 3 and 4.

5. *Twin loop,* a composite pattern constituted of two intertwining loops opening in different directions.
6. *Lateral pocket loop,* a composite pattern of two loops opening in the same direction.
7. *Central pocket loop,* a composite pattern consisting of a large loop enclosing a small whorl in the center.
8. *Double loop,* a whorl like pattern but with two intertwining loops within the core area that spiral around within the pattern.
9. *Twin whorl,* a distinctive type of pattern where only *one* radiant from each triradius enters the pattern, the other going around it to form an eye-like design.

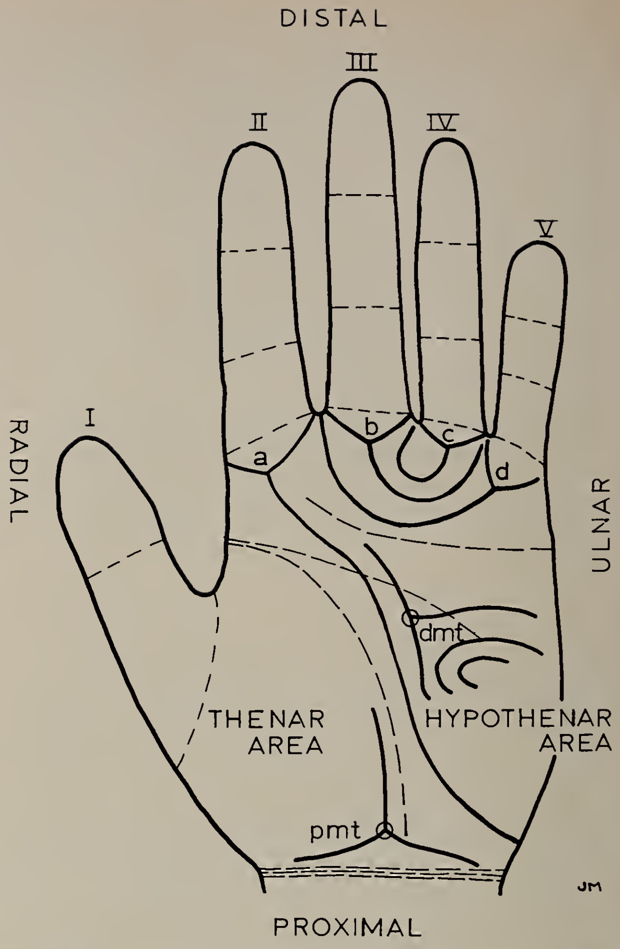

Figure 8.—Four triradii, points where three ridge systems meet, are found at the base of Digits II, III, IV and V, and are respectively designated *a, b, c,* and *d.* The proximal radiant from each of these triradii is called a main line and is traced across the palm to show ridge direction. The main lines are designated with capital letters. A triradius is observed medially at the base of the palm and is called the *proximal medial triradius,* to distinguish it from other medially placed triradii which are associated with patterns in the hypothenar area. Such triradii are called *distal medial triradii.* These triradii are referred to as *pmt* and *dmt.* Three flexion creases are seen on the palm. The longitudinal flexion crease starting above the thumb and enclosing the Thenar area, the Proximal transverse flexion crease starting at the same place and going across the palm and the one above it starting on the ulnar side of the palm which is referred to as the distal transverse flexion crease.

The interdigital patterned areas lie between the triradii at the base of the digits. Interdigital area I is always referred to in conjunction with the thenar area as *thenar I.* Interdigital areas II, III, and IV often show patterns, particularly loops.

Not all 18q− patients possess as unusually large patterns as reported for PM150864[25] but the tendency to large patterns is clearly demonstrated. The ridge count is elevated as direct result of the large size of the patterns. The distal half of the palm is more affected than the proximal area of the palm. The patterns observed in the thenar/first interdigital area and the hypothenar area do not appear to be affected. The proximal medial triradius, the pmt, appears normal.

The transverse flexion creases of the palm do not fuse to form a single transverse flexion crease but show a tendency to run minor lines towards each other thus resulting in transitional forms.

Both triradii *a* and *d* are displaced radially. Triradius *d* by being thus displaced moves towards the center of the palm and results in its proximal radiant, Main Line D, traversing the palm in a transverse fashion. This feature has also been noted by Plato et al.[26] However, the same radial displacement moves triradius *a* towards the radial border thus resulting in Main Line A traversing the palm in a longitudinal fashion.

Summary

This is a description of two children who have a deletion of the long arms of chromosome 18. They are mentally retarded and they demonstrate some of the phenotypic features of the syndrome. The associated anomalies are subtle and are not diagnostic. The serum immunoelectrophoresis of the patients showed normal levels of IgA, IgG and IgM. The dermatoglyphic patterns are abnormal but are not diagnostic.

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A TEST FOR CORROSIVE ESOPHAGITIS

In patients with suspected corrosive esophagitis, the presence or absence of mouth or pharyngeal burns is not a sure indication of the presence or degree of esophageal involvement. The history obtained from these patients or excited parents is also unreliable. In our series 1021 patients with a history of ingestion of a potentially corrosive substance were "scoped"; 239 actual corrosions were found. The need for this examination is evidenced by these results. The unreliability of the history is also obvious. . . . The presence of ulceration and the need for treatment can be established only by esophagoscopy.

—John C. Cardona, m.d., New York City
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Special Article

On Those From Whom We Learn

JOHN ROMANO, M.D., *Rochester, NY*

GEORGE BERNARD SHAW remarked, "Those that can, do; those that can't, teach." More recently Sir Theodore Fox, long-time editor of the *Lancet*, added, "Those who can't teach like to talk about teaching, especially after dinner."

With this caution I shall do my best, if not about teaching, at least about learning. Learning is the most central and compelling purpose of the university—learning that takes place between teacher and student, teacher and teacher, student and student, and in the medical school between teacher and student and patient and family and others who care for the sick.

Whitehead said, "The central purpose of the university is the imaginative acquisition of knowledge," namely, learning. Learning can only take place, remain viable and grow if it is nourished by the pursuit of new knowledge and by the critical appraisal of today's information, knowledge and skills.

On an occasion like this it is appropriate to pay tribute to those from whom one has learned. It takes a little time, as Thoreau once said, for a man to fit his clothes. It takes a little time to become a physician and there are many who have taken part in the becoming—parents and spouses and peers and friends and teachers. Each deserves our warm gratitude.

But there are others to whom I wish to pay special honor. It is not often that they are thought of as teachers, but I have learned much from them and shall be grateful to them always. They are my students and my patients.

A teacher cannot be a teacher without a student; a man cannot learn to be a husband without a wife; a mother, without a child. Wordsworth's "The child is father to the man" tells us that the child takes his place in the education of his family. It is the responsiveness of the student, his engagement in the common task of acquiring knowledge; it is the mutuality of the experience which makes it possible for the teacher to fulfill his role.

The student offers challenge. I have the impression that I have learned more from the undergraduate medical student than from the graduate and resident group. The former are more apt to ask searching questions; perhaps being ahistoric their minds are not yet over-cluttered. The older group, at times, appear to have made their peace with ambiguity, at least they are more tolerant of our ignorances. I have learned that this may be an inevitable practice of the clinician, directly responsible for the sick, who must adopt a belief system freer from ambiguity than one who does not have this responsibility. I have learned from both groups. I have been stimulated by the frankness, the originality, the freedom and mobility of the younger minds not yet concerned with consequences, and by the growing maturity and judgment of their elders.

In the field of psychiatry, as in all other matters, the smaller the understanding of the situation, the more pretentious the form of expression, and I owe much to my students who have helped me distinguish between fact and fancy, notion and hypothesis. And they have impressed upon me the imperative need for clarity and to make every effort as best one can, to start our journey together from a point common to both. I know now that not all learn at the same rate. I learned, too, that some aspects of human biology, for example those that relate to bereavement, aggression, and sexuality, may cause more anxiety and concern in the learning process than does the counting of bones. This requires different methods of teaching, and it requires that student and teacher know each other.

Perhaps more important than anything else, students have taught me how to be responsible as a teacher. It is a serious matter, trying to influence the mind of another. The teacher must

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become responsible and accountable not only for learning proper methods of reaching the minds of his students but also for remaining informed in the field of his study—sufficiently informed so that he has some idea of the history of ideas and practices which have led to the present situation—sufficiently informed so that he is able to acquaint the student with points of view and evidences not necessarily sympathetic with the teacher's beliefs and convictions.

This leads me to tell you about my patients—what have I learned from them? I could not count the ways, much less the lessons learned. As one cannot become a teacher without a student, one certainly cannot become a physician without a patient. And this brings to mind the most essential ingredient, the physician's capacity to be concerned with the distress of another. Without this, the physician who serves as clinician cannot fulfill his obligation. You may remember the story attributed to Toscanini. The scene, the rehearsal of the orchestra during which the maestro is fascinated by the facial expressions of his concert master. He saw anguish, distress, sadness, all of which led him to stop and ask, "What is it, Giovanni, do you not like Beethoven?" With gloom and despair the concert master answered—"Maestro, it is not that I don't like Beethoven, it is just that I don't like music."

Fortunately, medicine is a house of many mansions. There are worlds of things as well as worlds of persons, and there is much for all of us to do. If, however, the physician is to be a clinician, one who cares for the sick and has direct responsibility for him, he must have what has been called the capacity for human intimacy—a basic capacity for interest in and involvement with oneself and with others. And this capacity, a necessary but not a sufficient condition, must be adapted to the specific tasks of the clinician.

The patient teaches us humility. In spite of exponential increases in information and knowledge, the acquisition of new skills with new technology and an endless number of new and promising drugs, we often are confronted with problems with which we realize how limited is our understanding, how imprecise our intervention. We, too, have our doctor's dilemma. At one horn we realize the limits of our knowledge and skill; at the other, we realize we must act now. We do not have the leisure of the spectator of the human comedy like the historian or philosopher or biochemist. The clinician must act, using the best knowledge and tools available to him.

The patient teaches us, too, to listen to him and to look at him. In psychiatry we have been so fascinated by what we hear that we have neglected to look. We can well respond to the wisdom of that Dean of Malapropisms, Yogi Berra, when he said "You can observe a lot just by watching."

It is only by listening and looking and by conducting relevant procedures that we learn the nature of our patient's distress. Our primary loyalty as clinician is to the patient, to the understanding of his distress and to its relief and not to our personal needs, beliefs, ideologies or chosen preferences for favorite drugs or modes of treatment. Sir Thomas Browne cautioned us over 300 years ago when he said, "I desire rather to cure his infirmities than my own necessities." This is particularly timely today when so many of us appear to be unduly concerned about our personal comforts as physicians and when we champion beliefs or schools of thought which bear little relevance to our patient's problems. I have learned to try to understand clearly what is the patient's problem and particularly his perception of his need. I have heeded the advice given me by a patient harassed and fatigued from years of pyschotherapy with and without drugs when he said, "You don't need to grind the valves every time; most often all I need is to have my windshield wiped."

Out of these experiences patients have taught me the necessity of the open mind, not open in the sense of being empty, but a mind open to constant critical review of what is known and yet able to entertain new information—a mind not enslaved by *a priori* views but prepared to make decisions appropriate to the specific needs of the patient.

What Holmes said of law, "It is a window through which one may look out upon mankind," is certainly true for medicine. My patients have added immeasurably to my education. I have learned about the crafts and the professions and the arts, of business and commerce and play and vice—of the manners and morals of men and women of our time. I have tried to avoid the preferential exclusion of attending to a limited sample of patients. It is said that the modern physician, particularly the psychiatrist, is apt to choose as his patients those whom he resembles most; and, as many of us are middle class and verbal, they are the patients seen. Voltaire said, "If a camel had a god, it would probably look something like a camel." I have cared for and been informed by patients black and white, rich and poor, young and old, harsh and gentle, and I assure you it has been a liberal education.

Patients have taught me of the ubiquitous presence of anxiety and depression in the experiencing of illness. They have added immeasurably to my knowledge of the psychology and sociology of illness and of convalescence. Over a century ago Charles Lamb, from his long experience as a patient wrote: "How sickness enlarges the dimensions of a man's self to himself! He is his own exclusive object." Although the expression of anxiety and depression may vary considerably, one learns that a common mechanism is that of self-absorption and retirement from reality. There are those who, like André Gide, believe that illnesses are the keys that can open certain doors for us. He wrote: "I believe that there are certain doors that only illness can open. There is a certain state of health that does not allow us to understand everything and perhaps illness shuts us off from certain truths; but health shuts us off just as effectively from others or turns us away from them so that we are not concerned with them."[1] But I find it difficult to glorify illness as such. My experience has taught me that illness, like poverty or bigotry, diminishes man. What ennobles man is not the illness but his response to the illness, and I have been immensely impressed by man's capacity, in legion ways, to master illness and distress in his attempt to regain health.

I believe Hemingway once defined courage as grace under pressure. I have seen this many times in the conduct of my patients. The courage of some patients is more visible, perhaps more public or more transmissible than that of others. Most of us are familiar with the remarkable achievements of the blind and the deaf. Many of you have read the personal documents written by orthopedically disabled persons such as Hathaway's THE LITTLE LOCKSMITH[2] or Carlson's (the spastic) BORN THAT WAY.[3] These and others are dramatic and moving documents and attest the perseverance and courage of the disabled patient.

In my work I have been impressed with the often silent and private courage of many psychotic patients, harassed and distressed for years by hallucinated voices. Recently a 40-year-old women, mother of four children, on her fifth admission for a recurrent psychotic experience, was asked about her voices and she replied: "I have been hearing these voices for over 20 years. At times they are soft, most often they are harsh. Even when soft, they appear to be angry and they provoke and tease me. What do you think it means to have heard these voices all of these years? They are with me when I awake in the morning. They were there when I changed the diaper of my child, when I tried to make a cup of tea or to pay the gas bill or to talk to a neighbor. There has been no rest. I don't know how or why I have stood it, but I felt I should go on living."

What is impressive is that so many do go on living; but there are others who cannot stand it. In Leonard Woolf's autobiography, published posthumously, he included Virginia Woolf's last note written to him before she killed herself by walking into the sea (March 28, 1941).[4] She wrote: "I am certain that I have gone too far this time to come back again. I am certain now that I am going mad again. It is just as it was the first time. I am always hearing voices, and I know I shan't get over it now. I shan't recover this time. I begin to hear voices and I can't concentrate, so I am doing what seems to be the best thing to do . . ."

And this brings to mind the prodigious variability of human behavior. We find variability, both intra- and inter-individual in biology as every biological scientist and medical clinician can attest. It is even more profound in the behavioral sciences and it is for this reason that we have had to develop modes of observation appropriate to our task of understanding behavior. As David Shakow has pointed out, medicine, as it includes biology and behavioral sciences, involves the observation of human beings by other human beings.[5] This makes necessary not only traditional objective observation but participant, subjective, and self-observation. In addition, the student and the physician learn that this differentiation between the several types of observation is central to the understanding of the patient-physician relationship and to the series of human events which take place between them.

I am grateful to many patients for their kindness and compassion and generosity. Innumerable instances come to mind, particularly in my salad days, as student, as intern and as resident, of patients being kind and helpful. When I consider it now, I must have been falsely confident of my recently acquired professional role. Patients quite properly could have been much more critical of my behavior, but most were gentle and kind.

But, gratifying as my experience has been, it does not match that told me by Dr. Louis Hamman of Baltimore. He was the greatest clinician I have ever known. He was a wise, gentle, effective, and kind physician with immense experience, and his students at the Hopkins bless him for all that he gave of himself to them. I met him at a rather critical time in the lives of many of us. It was shortly after Pearl Harbor and our beloved Professor and Chairman of the Department of Medicine at Harvard and the Peter Bent Brigham Hospital had died fairly suddenly of a subarachnoid hemorrhage. The Harvard medical unit had been sent to Northern Ireland and to Australia and the destinies of many of us were quite uncertain. It was at that time that Louis Hamman came as Physician-in-Chief *pro tempore* to take over the duties of the hospital for a week's period, which is an old custom at the Brigham hospital. While I had known of Hamman for years, I had never had the opportunity to know him well, and we talked together on many matters. He was of tremendous help to us at that difficult time and did much to reduce the anxiety and the uncertainty of those of us left in the hospital. One day we were speaking about how much one did learn from patients. In that setting he told me this story.

"It happened to me many years ago. I had just finished the residency in medicine and Dr. Thayer, who was then Professor of Medicine at the Hopkins, called early one morning to ask if I would take his professorial rounds at the Hopkins that day. Thayer had been called on an emergency basis to see a VIP in Washington and he did not have time to make other arrangements. I was delighted and very honored and quite anxious but finally succeeded in shaving without cutting my throat and did appear at the proper time at the hospital floor, where news of my coming had been spread. There faced me a semicircle of faculty, students, nurses, and peers with that same leer on their faces that a substitute 5th grade teacher finds as she enters the room. I can assure you those facial expressions did not help and, to make matters worse, as I walked toward the first patient on the left, the crowd surrounded me completely. I shall never forget, nor fail to be eternally grateful to that first patient. For when I leaned over to examine him he whispered in my ear, 'Heart's on the right side.' "

Can you think of anyone's being kinder than that?

As Sigerist has pointed out, throughout the centuries the medical ideal has changed greatly in the course of time and is evolving constantly: "The physician was a priest in Babylonia, a craftsman in ancient Greece, a cleric in the early and a scholar in the later Middle Ages. He became a scientist with the rise of the natural sciences, and it is perfectly obvious that the requirements put upon the physician and the tasks of medical education were different in all those periods."[6] Whatever image the physician may have had in the society which he served, certain qualities have remained transcendent, qualities which made for responsibility, dependability and accountability, qualities which made possible the compassionate objectivity of the clinician in his care of the sick. They have remained transcendent because our patients have insisted that we have the knowledge and the skill and the devotion to care for their needs, to reduce their suffering, to prolong their lives, and, when possible, to prevent their distress. In our time, as in other times, these qualities must be acquired by the physician. In our time, different from other times, there may be a special and urgent need to ensure that the medical student be prepared appropriately and usefully for his time.[7]

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Medicine and the Maelstrom

The Debate on American Health Care

JEAN F. CRUM, M.D., *President, California Medical Association*

IN MY ROLE AS A SPOKESMAN for the California Medical Association, I spend most of my time speaking to groups of other doctors or to groups of politicians. In either case, I often find the audience biased on the subject of medical care. So you can understand that I welcome this chance to talk to a more diverse audience.

As the Health Problems Committee of the Commonwealth Club is well aware, American health care and medical care have become subjects of national debate in recent years. Looking through recent issues of magazines or newspapers, it would seem that the country has been inundated with experts on health care. And some are insisting that drastic changes are necessary in our system of delivering health care.

It is valuable to examine for a moment why some people are advocating a complete restructuring of our present approach to health and medical care. Perhaps the major argument used is that the level of health care in the United States ranks far below that of a number of other countries, especially some smaller ones in Western Europe. For instance, the following statement appeared not too long ago in a national magazine:

> The state of our nation's health is bad. We rank far below less affluent countries. In infant death rates, the United States stands tenth; in death from diabetes, fourteenth; from heart disease, thirteenth; in overall death, fifth. And in prolonging life, we are eighth.

A similar observation was made about the same time by Senator Jacob Javits in a letter to the *New York Times*. He said:

> Our nation has unchallenged leadership in biomedical research and medical technology. Yet among the nations the United States ranks thirteenth in infant mortality, eleventh in maternal mortality rates and twenty-second in life-span for men.

These are easy, "simple" arguments to present, and they sound convincing to the general public. But they contain a number of fallacies. I draw your attention to the two differing figures used for infant mortality rates in these two quotes, ranking the United States tenth and thirteenth respectively. The fact that they *are* different is significant. In recent reports and articles, the relative position of the United States in regard to infant mortality has varied from sixth to 28th—depending on the person or agency doing the reporting.

The inconsistencies originate from a number of sources. They may spring from the use of different sources for the figures on infant mortality for a given country. And different countries use different ground rules for collecting and listing health statistics.

This leads us to an important question: How do you measure how effectively a health care system meets the needs of the people?

We believe that general health, growth and development, improved life expectancy, eradication of infectious disease, elimination of contagious disease such as poliomyelitis, tuberculosis, typhoid fever and tetanus, advances of medical and surgical techniques for the early detection, treatment and cure of heart disease, stomach ulcers, cancer and other killer diseases, are yardsticks by which good medical care can be measured. By all of these standards, medical care in this country excels.

In recent years, some have attempted to equate levels of infant mortality with the effectiveness of our health care system. This fallacy needs to

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be dispelled. Sweden, with the world's lowest infant mortality, has the world's greatest mortality from stomach ulcers and the second highest from pneumonia. Most studies reveal clearly that excess infant mortality is rooted in poverty, malnutrition and racial discrimination. Infant mortality in fact, correlates best with the level of education achieved by the mother. As we grapple with these social ills, our infant mortality rates have sharply declined.

Deficiencies but Not "Crisis"

This is not to say that our present system is perfect. It contains some very real inadequacies. Some people who need care go without it—because they cannot afford it, because it simply isn't available to them, because they don't know how to obtain it, or because they lack adequate education to use what is available. Catastrophic illness may occur at any income level, creating serious financial problems. Some people living in remote rural areas or urban ghettos have no readily available access to the health care system. In addition, government health programs promise full health care, but seldom budget enough to provide it. For example, California's Medi-Cal program for the poor has not achieved its objectives—despite the fact that this fiscal year California doctors, in effect, are subsidizing Medi-Cal by about $61-million because of substandard reimbursement of fees under the program. But all these factors do not constitute a health care "crisis"—as is sometimes alleged. Rather they represent deficiencies that must be eliminated.

The basic fact that the quality and quantity of medical services in the United States is now at an all-time high, and in the aggregate, favorably compares with the situation in any other nation in the world cannot, and should not, be ignored. Then too, it should be recognized that mortality and morbidity rates in the United States are at the lowest levels ever, and the situation in this respect is continuing to improve. Therefore, it is apparent that our need in this country is not to restructure drastically or further control or destroy our system of medical care—as some critics would have us do. Instead the need is to expand it so that it is within reach of those who do not now receive its benefits and services. In other words, we must fill the gaps in our present system without discarding those aspects in which it traditionally does a good job.

Freedom of Choice

Americans today have the finest system of medical care ever available anywhere in the world. Our goal should be to provide access to this high quality medical care for everyone. We believe that medical care can be delivered best when both patients and physicians have complete freedom of choice . . . when each doctor can assume full responsibility for his own patients, and exercise his knowledge, experience, skills and judgment, free from outside interference. We believe that this freedom of choice for patient and doctor can only be preserved by our voluntary private system.

A former Secretary of Health, Education and Welfare, John Gardner, in commenting about this situation, recognized the necessity and the value of change but added: "This is not to say that we must be infatuated with everything new and reject everything old. In all evolutionary growth there is a complex interweaving of continuity and change. One of the purposes of social change is to find new solutions that will preserve old values. When the spring dries up, the farmer seeks a new source of water, not for the love of novelty but to bring himself back into balance with his environment."

We who are concerned with medical care in this country must find answers to some important questions. How do we go about finding "new solutions that will preserve old values?" What "old values" do we wish to preserve?

Certainly we wish to preserve the traditional stress placed on quality care. Maintaining and improving the present high quality of medical care have long been areas of intense concern for the medical profession. In this day of increasing demand for services and the increased role of third parties, these activities remain a major concern.

As in other areas of the nation, physicians in California have approached the subject of assuring quality care through a system of "peer review." California Medical Association and the county medical societies have standing peer review committees—hundreds of experienced physicians who volunteer their time to review the quality and appropriateness of the medical care other doctors provide for their patients. Among many other aspects, I might mention the work of hospital tissue committees in reviewing indications for surgical operation, the survey teams that review hospital medical staffs and the committees reviewing medical care in nursing homes.

In addition, the role of peer review has been expanded into the area of cost control—evaluating the medical charges made by a physician. A third and related objective of peer review activities is to promote effective utilization—to discourage unnecessary laboratory tests or excessively long hospitalization. Another important aspect is to deal, on the patient's behalf, with underutilization. This obviously can be more serious for the patient in maintaining high standards for his care.

Continuing Medical Education

Another approach we are taking in California to insure continued high quality care is the California Medical Association's program to certify physicians' continuing medical education. To be certified, physicians must participate in a minimum of 200 hours of continuing medical education in a three-year period. The CMA provides specific mechanisms for accreditation of continuing educational programs and acts to improve educational quality and make it more effective as a means of improving patient care.

It also should be noted that the medical profession is actively seeking ways to eliminate health care deficiencies that do exist, without sacrificing the already high level of medical care we have achieved in this country. Many new and innovative approaches to the delivery and financing of medical care are being studied in California—and throughout the nation.

The California Medical Association feels that the "pilot project" is a particularly useful tool in this regard. This is a method of judging the effectiveness of new approaches through a controlled, small-scale trial project. For example, a San Joaquin pilot program is studying whether the state's Medi-Cal program for the poor can be improved by putting providers' services on a prepaid basis. The project hopes to determine whether a greater percentage of the eligible persons would be seen by a greater proportion of physicians under this approach. If so, then this method would assure quality medical care and—at the same time—perhaps supply it for less cost.

In our efforts to make good medical care available to everyone in the state, we are using a variety of approaches, and I'll cite just a few examples.

Better Distribution of Physicians

CMA maintains a Physician Placement Service created specifically to place physicians in locations where medical services are needed. We all have heard references to a "physician shortage" in this country—but recent information indicates that solving our health manpower problem is more a matter of better distribution than finding new ways to increase the number of physicians. According to the recent President's Manpower Report to Congress, by 1980 there will be about 440,000 physicians in this country—enough to eliminate the alleged doctor shortage. This figure represents a predicted ten-year increase of 120,000 physicians, using present educational approaches. Stated another way, the present proportion of 157 doctors for every 100,000 people will increase to 180 doctors per 100,000 people by 1980. Also in regard to the alleged doctor shortage, it should be noted that the overall number of physicians in this country is increasing at a rate three times that of the general population growth.

Our component county medical societies are active with projects on the local level. Shasta-Trinity County Medical Society has developed a unique emergency care program. The San Francisco Medical Society is working with the Office of Economic Opportunity in bringing medical care programs to the inner city. Kern and Sacramento County Medical Societies are operating clinics to bring medical treatment to rural migratory workers. Monterey County Medical Society is the fiscal agent for a pioneering rural "health care team" approach that covers a wide area around King City. The Los Angeles County Medical Association is doing innovative work in such areas as peer review and extended care surveys. Other county medical societies—in the ways they find best suited to local needs—are seeing that health care is brought to migrant agricultural workers, into rural areas and urban ghettos.

The foundation for medical care is another approach being taken by the medical profession—and one in which California has led the nation. These foundations are non-profit organizations of doctors sponsored by local county medical societies. They are concerned with the development and delivery of medical services at a predictable cost, whether it be privately or publicly financed.

These are a few of the approaches being taken by the medical profession to improve our system of health care.

Nonetheless, as much as the medical profession—or any other single group—is doing to seek solutions, these problems sometimes transcend the resources available to us alone.

All of this leads me to another important consideration. It is necessary that we Americans rethink some of our ideas about improving *health* care. Americans usually fail to consider that there are other factors even more influential than *medical care* in a nation's health. Specifically, environmental factors; inadequate general health education; automobile and home accidents; poor housing, sanitation and nutrition; obesity; alcoholism and drug abuse; cigarette smoking; suicide, homicide and other violent crimes are all factors to which our nation has devoted too little attention. Instead of making concerted efforts to solve these problems, we too often have fallen victim to the idea that new programs of government financing will somehow magically eliminate all health-related difficulties. Obviously, this simply is not so. The present major difficulties being experienced nationally by the Medicare program for the elderly and the Medicaid program for the poor testify to that fact.

The Future for Medical Care

This encapsulates the present situation. But what of the future? What does the future hold for medical care in this country?

Some hospital spokesmen foresee the rise of the hospital as a center of medical care. Stephen Morris, the president of the American Hospital Association, is one of the advocates for changing the role of the hospital. However, there are serious deficiencies in any proposal that promotes the corporate practice of medicine—as embodied in this concept of the hospital as the center of care. To state an obvious fact, the purpose of any system of medical and health care is to bring together one patient who needs medical care and one physician who can see that he receives care. It can never be forgotten that medical care is given to one individual at a time. In the final analysis, only physicians can deliver medical care. And any approach to medical or health care that neglects this fact cannot adequately serve the needs of the patient.

The current debate about national health insurance undoubtedly will play an extremely important role in determining what the future holds for health care in this country. Sixty-two health insurance bills have been introduced in the House of Representatives this session. Another dozen, some similar to House legislation, are in the Senate. However, it seems unlikely that a program of national health insurance will pass in the immediate future. Congressman Wilbur Mills, chairman of the powerful House Ways and Means Committee—the committee through which such proposals must move—has made some interesting observations in this regard. He has said that he believes the period of time necessary to consider national health insurance is not available this year, and therefore his committee probably will not start considering proposals until 1973. Moreover, he has said it is not possible at this time to establish what priority national health insurance would have next year before the committee.

Improving What We Have

Nonetheless—unless there is a change in public and political sentiment—it looks like some increased involvement of government in health care probably will take place within the next few years. Strictly defined, national health insurance is a program for financing almost all health care services for the vast majority of the population of a country through a governmentally-administered insurance system. Of the major pending proposals concerning national health care, only two are strictly national health insurance—the Kennedy Bill and the Javits Bill. Other proposals, such as those of the Nixon Administration, the American Medical Association, and the Health Insurance Association of America, generally would build upon—rather than destroy—the existing health insurance and delivery structures. Such plans recognize that it is much better to utilize and develop a health care system that is now providing reasonably adequate protection to some 80 to 90 percent of the population than to inaugurate a new system of unproved quality and capability. Similarly, proposals for catastrophic insurance alone—such as those of Senator Long and Congressman Hall—would utilize the existing administrative and delivery systems.

"Ameriplan," a proposal developed by a committee of the American Hospital Association, which later withdrew its support, has recently been submitted by Congressman Ullman of Oregon. It would have a significant effect on the medical care delivery system since it would center such services in "health care corporations" and would thus eliminate solo and small-group practices from the scene.

The administration's proposal for national health insurance—known as the National Health Insurance Standards Act—has as a basic feature the establishment of "Health Maintenance Organizations." In addition, various members of Congress have also proposed their own concepts of what constitutes an HMO. Currently, three major HMO bills are being considered by the Senate Health Subcommittee. The specific nature and scope of the HMO concept in the future, therefore, depends on what legislation in this field Congress decides on.

Exactly what is an HMO? First, it is a form of contract group practice. Based on bills before Congress, an HMO must assume legal responsibility for providing a broad range of health care services, including both professional and institutional services, and accountability for both the quantity and quality of services provided. An HMO would provide emergency care, hospital and physician care, ambulatory physician care and outpatient preventive medical services.

Payment for such services must be on a prospective capitation basis. Individuals or families must pay a monthly fee in advance with the fee ordinarily set for a period of at least a year at a time.

Let us examine the merits of the HMO concept. We feel that it is possible the HMO approach *may* provide one method of solving health problems. However, we note that the administration has already made some 110 grants for planning and feasibility studies for HMOs. The results from these studies are not yet in. They have not yet provided essential data regarding the quality and extent of services that can be provided, their accessibility to beneficiaries, the cost of providing them, and their acceptability to both consumers and providers. We can only conclude that any legislation to implement a concept which is still undergoing testing would be unwise and premature.

Professional Standards Review

The Professional Standards Review Organization—or PSROS—is another legislative concept that could fundamentally affect our present approach to health care. Introduced by Senator Bennett as an amendment to the Social Security bill, the PSRO approach would establish a governmental program of peer review. Stated briefly, non-profit organizations would be established in local areas to decide whether care provided under Medicare and Medicaid is medically necessary and to determine whether it measures up to professional standards.

We feel this approach has serious drawbacks. First, it would bring large-scale federal involvement into a function already successfully being performed by the medical profession. Furthermore, it would bring with it unnecessary and possibly harmful federal government controls. For instance, the amendment delegates almost complete authority over the program to the Secretary of Health, Education and Welfare. HEW would be allowed to set up regional norms and standards for medical care that would be subject to control by a National Professional Review Council and thus subject to the possible imposition of national standards—ignoring differing local circumstances and needs. In addition, PSROS—as proposed—would bypass one of the California Medical Association's most effective activities, the medical staff survey program.

Any one of these proposals we have discussed could have a fundamental effect on the future of medical care in this country.

As we have illustrated here, the medical profession continues to be very active in attempting to find solutions to the deficiencies in America's health care system. We have identified the problems as being concerned with access, quality and cost of care. And we have tackled these problems voluntarily—building on the strengths of the health care system of the private sector that has been responsible for this country's greatness. This voluntary approach is indeed an important aspect of our American system and one of the hallmarks of its success. It is important therefore that organizations concerned with health care remain independent of government control, remain responsive and close to the people. This is our belief and the basis of our activities. We are preparing for the future by dealing with the problems of the present—ever mindful of the fact that our primary obligation remains the best interest of our patients.

List of Organizations Approved for Courses Qualifying for Category I Credits in CMA Certification Program

■ *The following organizations, societies and institutions have been approved for Category I (formerly Group A) credit towards the California Medical Association's certificate in continuing medical education program. The credit hours are based on the number of hours of the course. Only those courses which are directly related to medical education and applied to patient care are acceptable. Courses put on by approved institutions, in subject matter not directly related to patient care and medical education, are not eligible for Category I credit in the program.*

This listing is not all-inclusive, as new programs are continuously being accredited, but it is up to date of as August 1, 1972. Physicians should refer to this listing when completing their annual reporting form.

Acceptable for Category I Credit Towards the California Medical Association's Certificate in Continuing Medical Education as of August 1, 1972

1. All formal programs sponsored by American Medical Association-approved medical schools in the United States and Canada.
2. Specialty societies and their California affiliates, formally recognized by the AMA or the California Medical Association.
3. AMA or CMA accredited institutions, hospitals, and organizations.
4. Formally constituted meetings, courses, programs at schools of public health.

Academy of Psychoanalysis
Academy of Psychosomatic Medicine
Aerospace Medical Association
Alameda-Contra Costa OB/GYN Society
Alta California Ophthalmologic Society
American Academy of Allergy
American Academy of Cerebral Palsy
American Academy of Child Psychiatry
American Academy of Dermatology
American Academy of Facial, Plastic & Reconstructive Surgery, Inc.
American Academy of General Practice
American Academy of Neurological Surgery
American Academy of Neurology
American Academy of Occupational Medicine
American Academy of Ophthalmology & Otolaryngology
American Academy of Orthopaedic Surgeons
American Academy of Pediatrics
American Academy of Physical Medicine & Rehabilitation
American Association for Clinical Immunology and Allergy
American Association for the Surgery of Trauma
American Association for Thoracic Surgery
American Association of Genito-Urinary Surgeons
American Association of Neurological Surgeons
American Association of Obstetricians & Gynecologists
American Association of Pathologists & Bacteriologists
American Association of Plastic Surgeons
American Broncho-Esophagological Association
American Cancer Society
American Clinical & Climatological Association
American College of Allergists
American College of Angiology
American College of Cardiology
American College of Chest Physicians
American College of Gastroenterology
American College Health Association
American College of Obstetricians & Gynecologists
American College of Physicians
American College of Preventive Medicine
American College of Radiology
American College of Surgeons
American Dermatological Association, Inc.
American Diabetes Association
American Electroencephalographic Society
American Fracture Association

Reprint requests to: Certification Program, California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

American Gastro-Enterological Association
American Geriatrics Society, Inc.
American Gynecological Society
American Heart Association, Inc.
American Industrial Hygiene Association
American Institute of Ultra Sound in Medicine
American Laryngological Association
American Laryngology, Rhinology & Otology Society
American Neurological Association
American Ophthalmological Society
American Orthopaedic Association
American Otological Society, Inc.
American Pediatric Society
American Physicians Fellowship, Inc.
American Proctologic Society
American Psychiatric Association
American Psychoanalytic Association
American Psychopathological Association
American Psychosomatic Society
American Public Health Association
American Radium Society
American Rheumatism Association
American Roentgen Ray Society
American Society for Clinical Investigation
American Society for Clinical & Experimental Hypnosis
American Society for Experimental Pathology
American Society for Surgery to the Hand
American Society of Abdominal Surgeons
American Society of Anesthesiologists
American Society of Clinical Hypnosis
American Society of Clinical Pathologists
American Society of Cytology
American Society of Internal Medicine
American Society of Ophthalmologic & Otolaryngologic Allergy
American Society of Plastic & Reconstructive Surgery
American Surgical Association
American Thoracic Society
American Urological Association
Armed Forces Institute of Pathology
Association of American Medical Colleges
Association for Research in Ophthalmology
Association of American Physicians

Biennial Western Conference on Anesthesiology

California Academy of Preventive Medicine
California Blood Bank System
California Hospital Medical Center, Los Angeles
California Radiological Society
California Society of Allergy
California Society of Anesthesiologists
California Society of Internal Medicine
California Society of Pathologists
California Society of Plastic Surgeons
California Society of Physical Medicine and Rehabilitation
California State College Physicians Association
California Thoracic Society
California Tuberculosis & Respiratory Disease Association
California Tumor Tissue Registry, and Valley Study Group
Canadian Ophthalmological Association
Cedars-Sinai Medical Center, Los Angeles
Center for Training in Community Psychiatry and Mental Health Administration
Central Association of Obstetricians & Gynecologists
Central California Psychiatric Society
Central Neuropsychiatric Association
Central Society for Clinical Research
Central Surgical Association
Cordes Eye Society of University of California Medical Center, San Francisco
Chapman General Hospital, Orange
Children's Hospital of Los Angeles
Children's Hospital of Long Beach
Children's Hospital of Orange County
Children's Hospital, San Francisco
Cleveland Clinic Educational Foundation
Clinical Orthopaedic Society
College of American Pathologists
Congress of Neurological Surgeons
Cook County Graduate School of Medicine
Commission on Professional Hospital Activities, Ann Arbor, Michigan

Department of the Air Force, Div. of Medical Education, Washington, D.C.
Department of the Army, Office of the Surgeon General, Washington, D.C.
Diabetes Association of Southern California

East Bay Psychiatric Association
East Bay Radiological Society
Endocrine Society
Estelle Doheny Eye Foundation
Eureka Orthopedic Association

Federal Aviation Administration
Federation of American Societies for Experimental Biology
Federation of Western Societies of Neurological Science
Fifty Year Club of American Medicine
French Polyclinic Medical School Health Center
Fresno County OB-GYN Society
Fresno County Surgical Society
Fresno Surgical Society
Fullerton Community Hospital

General Hospital of Ventura County

Heart Association of the Redwood Empire
Hospital of the Good Samaritan, Los Angeles

Industrial Medical Association
Inland Radiological Society
Inter-American Radiology Symposium
International Academy of Pathology
International Anesthesia Research Society
International Cardiovascular Society
International College of Surgeons
International Society of Surgery—American Branch
Interstate Postgraduate Medical Association of North America

James Ewing Society

Kaiser Foundation Hospital, Hayward
Kaiser Foundation Hospital, Harbor City
Kaiser Foundation Hospital, Los Angeles
Kaiser Foundation Hospital, Oakland
Kaiser Foundation Hospital, Redwood City
Kaiser Foundation Hospital, Richmond
Kaiser Foundation Hospital, San Francisco
Kaiser Foundation Hospital, Santa Clara
Kaiser Foundation Hospital, Vallejo
Kaiser Foundation Hospital, Walnut Creek

Los Angeles County-University of Southern California Medical Center

Lahey Clinic Foundation, Boston
Leroy C. Abbott Orthopaedic Society
Long Beach Community Hospital
Long Beach Obstetrics & Gynecology Society
Los Angeles Allergy Society
Los Angeles County Society of Anesthesiologists
Los Angeles Dermatological Society
Los Angeles Foundation of Otology
Los Angeles OB-GYN Forum
Los Angeles OB-GYN Society
Los Angeles Ophthalmology Society
Los Angeles Pediatric Society
Los Angeles Psychoanalytic Institute
Los Angeles Radiological Society
Los Angeles Society of Pathologists
Los Angeles Surgical Society
Los Angeles Urological Society

Mayo Foundation for Medical Education & Research
Medical Media Network (UCLA)
Memorial Hospital, Long Beach
Metropolitan Dermatological Society of Los Angeles
Mills Memorial Hospital
Mid-Valley Radiological Society
Midway Hospital, Los Angeles
Mount Zion Hospital & Medical Center, San Francisco

National Communicable Disease Center, Atlanta
Norman F. Miller Gynecological Society
Northern California Allergy Society
Northern California OB-GYN Society
Northern California Psychiatric Society
Northern California Radiological Society

Obstetrical & Gynecological Assembly, Los Angeles
O'Connor Hospital, San Jose
Orange County Dermatology Society
Orange County OB-GYN Society
Orange County Radiological Society
Orange County Surgical Society
Orthopaedic Hospital, Los Angeles

Pacific Association of Pediatric Surgeons
Pacific Coast College Health Association
Pacific Coast Fertility Society
Pacific Coast OB-GYN Association
Pacific Coast Oto-Ophthalmological Society
Pacific Coast Surgical Association
Pacific Dermatologic Association
Pacific Hospital, Long Beach
Pacific Medical Center, San Francisco
Page and William Black Postgraduate School of Medicine
Pan Pacific Surgical Association
Peninsula OB-GYN Society
Phil Thorek Postgraduate Course, Chicago
Postgraduate Medical Institute, Boston
Postgraduate School of the New York Eye and Ear Infirmary

Radiological Society of North America
Radiological Society of Southern California
Redwood Empire Radiological Society
Reno Surgical Society
Research Study Club, Los Angeles
Riverside-San Bernardino OB-GYN Society
Roseville Community Hospital

Sacramento Pediatric Society
Sacramento Valley Dermatological Society
San Diego Allergy Society
San Diego Dermatological Society
San Diego Gynecology Society
San Diego Psychiatric Society
San Diego Psychoanalytical Foundation
San Diego Radiological Society
San Francisco Dermatologic Society
San Francisco Gynecological Society
San Francisco Psychoanalytic Institute
San Francisco Radiological Society
San Francisco Surgical Society
San Joaquin County General Hospital, Stockton
Santa Monica Medical Center
Sequoia Hospital, Redwood City
Shufelt Society of Santa Clara County
Society of Biological Psychiatry
Society of Graduate Surgeons, Los Angeles County Hospital
Society of Medical Consultants to the Armed Forces
Society for Adolescent Medicine
Society for Pediatric Radiology
Society for Surgery of the Alimentary Tract
Society of Head and Neck Surgeons
Society of Nuclear Medicine
Society of University Surgeons
Sonoma Valley Hospital
Sonoran Dermatologic Society
South Bay Pathology Society
South Coast Radiological Society
South Coast Hospital, Laguna
Southeastern Surgical Congress
Southern California Pediatric Postgraduate Course
Southern California Psychiatric Society
Southern California Psychoanalytic Institute
Southern California Radiological Society
Southern California Society for Child Psychiatry
Southern Surgical Association
Southwest Obstetrics & Gynecology Society
St. Joseph Hospital, USC, Burbank
St. Jude Hospital, Fullerton
State University of New York, Downstate Medical Center
Surgical Section, Los Angeles County Medical Association
Symposium Neuro-Radiologicum

The Southwest Surgical Congress
The Endocrine Society
Tri-County Dermatology Society
Tri-County Surgical Society of Southern California

University of Chicago, Div. of Biological Sciences & Pritzker School of Medicine
U.S. Naval Medical School

Valley Presbyterian Hospital, Van Nuys
Variety Children's Hospital
Ventura County General Hospital
Virginia Mason Medical Center

Walter Reed Army Hospital
West Coast Allergy Association
West Valley Community Hospital, Encino
Western Dialysis & Transplantation Society
Western Industrial Medical Association
Western Laboratories: Medical Legal Seminars
Western Neuro-Radiological Society
Western Orthopedic Association
Western Surgical Association
Woodland Medical Clinic Group
Woodland Memorial Hospital

PUBLIC HEALTH REPORT

Frederick B. Hodges, M.D., Director, State Department of Public Health

The San Francisco Bay Area Resource for Cancer Epidemiology

The selection of cancer as the focus of a major health program to be organized and financed by the Federal Government places particular emphasis on cancer epidemiology. Recently, the Biometry Branch of the National Cancer Institute selected the San Francisco Bay Area, comprising Alameda, Contra Costa, San Francisco, San Mateo and Marin counties, as a resource for cancer epidemiology. An administrative unit, the San Francisco Bay Area Resource for Cancer Epidemiology, is being established in the State Department of Public Health to provide the Biometry Branch of the National Cancer Institute with a mechanism to coordinate epidemiologic, biometric, training and related interests.

From the Bay Area's three million population there are more than 11,000 cancer cases each year. The total includes enough cases of most cancer sites for study purposes and contains sizable ethnic subpopulations having differing cancer risks, including whites, Chinese, Japanese, blacks, Spanish-Americans, Filipino-Americans, American Indians, Samoans and Guamanians. Schools of medicine and public health in the Bay Area have long been engaged in cancer research, epidemiologic study and training in epidemiology, and the Resource for Cancer Epidemiology will provide field training in cancer epidemiology for students.

The Resource for Cancer Epidemiology will combine the cancer epidemiology activities and the California Tumor Registry. Its activities will include cancer incidence determinations based on the five Bay Area counties serving as its geographic base, survival determinations, epidemiology and training.

Since 1960, the California Tumor Registry has accumulated incidence data from the Alameda County Cancer Registry, one of its units, covering the county's one million population. The registry is expanding incidence determination activity to include the entire five-county area, starting with cases diagnosed in 1972. This will increase population coverage for epidemiologic studies and sample sizes for incidence and survival computations, allowing inter-social class comparisons, as well as providing continuous current data on temporal, spatial and demographic trends in cancer incidence. The registry will carry out these activities through reporting of cases from the 73 hospitals that diagnose and treat about 11,000 new cancer cases annually. The California Tumor Registry will continue to work with hospitals throughout the state in its end results and survival data activities. The registry is a major contributor to the End Results Program of the National Cancer Institute, providing 40 percent of the data used by the Institute in the studies of survival of cancer patients.

The California Tumor Registry also conducts the San Francisco Bay Area section of the Third National Cancer Survey, collecting morbidity data for the five counties over the triennium 1969-71. A ten percent sample of cancer patients in the survey is interviewed for disability, medical care data, and related costs.

The cancer incidence determination system of the Resource for Cancer Epidemiology will collect case reports among Bay Area residents. They will provide essential information for planning and developing cancer epidemiologic studies to be carried out in the Bay Area, including determination of incidence rates, distribution, and ethnic sub-population comparisons.

The epidemiology section of the Resource for Cancer Epidemiology will carry out ad hoc cancer studies. It will develop data on environmental exposures and cultural practices of groups in the Bay Area, and offer the opportunity for collection of collateral data from laboratory studies of viral, genetic and cytologic nature, searching for clues to the causes of cancer. Representative studies might identify, for example, any influence of contraceptive drugs on breast cancer incidence; genetic, biologic, social or cultural differences in breast cancer incidence among the several Bay Area ethnic groups; infectious or chemical agents from certain males that may induce cervical cancer in susceptible women; anatomic, anthropologic, infectious or hormonal causes of nasopharyngeal cancers; and differences in cancer incidence among migrant (for example, Japanese) as compared with native populations.

A board of professional advisors composed of representatives from various institutions interested in cancer epidemiology will consider feasibility of study proposals. The epidemiology section will be accessible to all individuals and institutions in the area interested in carrying out cancer epidemiologic studies.

SYMPTOMS OF DARVON® INTOXICATION

Darvon® is a drug in which the presentation in massive overdosage is as likely to be seizures as coma. I recently saw a woman who walked into the emergency room at a hospital in the city and said she had taken 15 Darvon capsules. Her doctor gave her a little syrup of ipecac. Between the time he administered the ipecac and the time it worked, a space of about 15 minutes, the woman rapidly lapsed into coma, had two grand mal seizures and a cardiac arrest. I was contacted at that point and arrived in the intensive care unit about 5 minutes after the patient. At that time she was having repeated seizures, a very characteristic presentation. So coma, respiratory depression, convulsions, and cardiac arrhythmia are common findings in Darvon intoxication.

Since Darvon is a narcotic, its effect is very well counteracted by Nalline® (nalorphine). Give 1 to 2 mg of Nalline intravenously at once, and you'll find the patient will begin to breathe almost immediately—within a minute or a minute and a half; and the seizure disorder will calm down very rapidly.

In young children there is a very rapid development of cerebral edema. If you get a history of possible Darvon ingestion, you ought to give nalorphine and at the same time begin the use of measures to counteract cerebral edema. You can use Mannitol®, urea, hyperventilation, steroids, or whatever approach you generally use—at once. Then you ought to use routine anticonvulsant management until the seizures are controlled.

—Daniel T. Teitelbaum, m.d., Denver
Extracted from *Audio-Digest General Practice*, Vol. 18, No. 10, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Proposed CMA Constitutional Amendments

FOR ACTION IN 1973

Six Constitutional amendments were introduced in the 1972 House of Delegates. Under the terms of the Constitution, these amendments must lie on the table until the next regular meeting of the House of Delegates.

These proposed amendments are shown here for the information of the membership. In addition, the proposed Constitutional amendments are required to be printed in two issues of CALIFORNIA MEDICINE before they come before the House of Delegates for action.

* * *

ARTICLE II, SECTION 1—CLASSES OF MEMBERS

Constitutional Amendment 1-72 Committee G

Introduced by: Paul Scholten, M.D.

WHEREAS, "free choice" is a prime tenet of the medical profession; and

WHEREAS, "required membership" is directly contrary to this prime tenet; and

WHEREAS, the recent poll conducted by the CMA as well as referendums by component medical societies indicated the desire of a substantial group of physicians to exercise their "free choice"; now, therefore, be it

Resolved: That the Constitution of the CMA be amended to include the classification of Independent Member. Such member would pay full dues to his component medical society and receive full benefits therefrom; such member *may* join the CMA by paying full dues, from which he would receive full benefits; and, be it further

Resolved: That Article II, Section 1, be amended by adding the word in italics: "The members of this Association shall consist of Active, Associate, *Independent*, Honorary, Retired, Life and Affiliate members."

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

ARTICLE I, SECTION 3—VOLUNTARY MEMBERSHIP IN CMA AND AMA BY A MEMBER OF A COMPONENT COUNTY MEDICAL ASSOCIATION

Constitutional Amendment 2-72 Committee G

Introduced by: James W. Goettle, M.D.
Representing: Tulare County Medical Society

WHEREAS, the present bylaws of the CMA make membership in the AMA and CMA compulsory to all members of a component county medical society; and

WHEREAS, the medical profession has always vigorously defended the concept of "freedom of choice" in health care, but will not give this freedom of choice to its members as numerous other states now do; and

WHEREAS, freedom of choice has always been beneficial to professional people in the long run, for it makes the leaders of such organizations more responsive to members' desires as the history of our country has so demonstrated to the world; now, therefore, be it

Resolved: That the CMA Constitution be amended to read as follows: (Article I, Section 3) members of local county medical societies in the State of California have the freedom to decide individually whether they wish to join the CMA or AMA, singly or in combination.

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

* * *

ARTICLE I, SECTION 3—PROPOSED CALIFORNIA MEDICAL ASSOCIATION CONSTITUTIONAL AMENDMENT PERMITTING VOLUNTARY MEMBERSHIP IN CMA AND AMA BY A MEMBER OF A COMPONENT COUNTY MEDICAL ASSOCIATION

Constitutional Amendment 3-72 Committee G

Introduced by: Allan K. Briney, M.D.
Representing: Los Angeles County

WHEREAS, the present Bylaws of the California Medical Association make membership in the

California Medical Association and the American Medical Association compulsory to all members of a component county medical society; and

Whereas, we, as a profession, vigorously defend the principle of "freedom of choice" in health care, yet deny individual members of county medical societies the freedom of deciding whether or not they wish to belong to the California Medical Association or American Medical Association; and

Whereas, each physician is quite capable of deciding whether there are sufficient advantages or insufficient advantages to maintaining membership in all three organizations; and

Whereas, mandatory membership in one organization (CMA and AMA) in order to maintain membership in another (local medical society) significantly interferes with the privilege of setting priorities as to organizational commitments, such as belonging to specialty societies; and

Whereas, in forty states a local county medical association member may decide for himself whether he also wishes to maintain membership in the state and national medical associations; e.g., New York and Massachusetts; and

Whereas, professional liability insurance carriers have no requirements about California Medical Association or American Medical Association membership for coverage of a county medical society member; and

Whereas, in a free and democratic society it would seem reasonable and consistent that membership in all medical societies should be voluntary, with each society attracting members on its own merits; and

Whereas, when a local county medical association collects dues for a state and national medical association, the individual dues-payer tends to lump all these dues together as "county medical society dues", feeling he may not be "getting his money's worth"; and

Whereas, there is widespread feeling among local county medical association members that the CMA and AMA have long ago lost their "grass roots" contact and cannot speak authoritatively for the medical profession; and

Whereas, recent polls of the Los Angeles, Orange, San Diego and San Francisco County Medical Associations have overwhelmingly favored voluntary membership by an average of four to one, as opposed to compulsory membership; and

Whereas, a national poll by *Medical Opinion* magazine, published in November, 1971, showed 82% favoring voluntary membership in the American Medical Association; and

Whereas, results of the recent CMA opinion poll are inconclusive and misleading, due to substitution of the words *involuntary* and *compulsory* specified in Bylaws Amendment 22-71 authorizing the poll, by the words *separate* and *unified;* now, therefore, be it

Resolved: That Article I, Section 3, be amended as follows:

> This Association is an organization composed of the component societies and their members who are members of this Association, the House of Delegates, the Council, the Scientific Board, the Scientific Assembly, Bureaus, Commissions and Standing Committees.

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

* * *

ARTICLE III, PART A, SECTION 1(d)—VOTING PRIVILEGES FOR SCIENTIFIC BOARD REPRESENTATIVES IN THE HOUSE OF DELEGATES

Constitutional Amendment 4-72 Committee G

Introduced by: Council

Resolved: That Article III, Part A, Section 1 (d)—House of Delegates composition shall be amended by deleting the words in brackets and adding the words in italics, so that this Subsection shall now read:

"(d) Ex officio, [without] *with* the right to vote, [eighteen (18)] *twenty-one (21)* members of the Scientific Board selected as provided in the Bylaws; and . . ."

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

* * *

DELEGATES AND ALTERNATES TO AMA SHALL BE EX OFFICIO DELEGATES OF CMA

Constitutional Amendment 5-72 Committee G

Introduced by: Lawrence E. Reck, M.D.
Representing: 1st District

Resolved: That Article III, Part A, Section 1, be amended by adding a new sub-section (f) which reads as follows:

(f) *Ex officio, without the right to vote, the officers, the delegates and alternate delegates to the American Medical Association, who are not otherwise members of the House of Delegates of this Association.*

ACTION: Adopted above substitute Constitutional Amendment No. 5-72 as substitute for Resolution No. 62-72. Tabled for one year. To be acted upon at the 1973 House of Delegates.

ARTICLE III—GOVERNMENT OF THE ASSOCIATION
PART A—HOUSE OF DELEGATES—COMPOSITION
SECTIONS 1, 2, 4

Constitutional Amendment 6-72 **Committee G**

Introduced by: E. Kash Rose, M.D.

Resolved: That Article III, Part A, Section 1, be amended by adding a new sub-section (g) which reads as follows: *(g) Delegates elected by duly enrolled medical students in good standing at accredited schools of medicine in California;* and, be it further

Resolved: That Article III, Part A, Section 2, be amended by adding the words in italics, to read as follows:

As the Bylaws shall further provide, the duly enrolled medical students in good standing at each accredited school of medicine located in California shall be entitled to elect one delegate from each such school; and, be it further

Resolved: That Article III, Part A, Section 4, be amended by adding the words in italics, to read as follows:

Delegates and alternates elected from each school of medicine shall serve for a term of one year.

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

SCIENTIFIC EXHIBITS

102nd Annual Session of the

California Medical Association

and Second Western States Invitational Scientific Assembly

March 10-14, 1973 **Disneyland Hotel, Anaheim**

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1973 Annual Session

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and Second Western States Invitational Scientific Assembly

March 10 to 14, 1973 • Disneyland Hotel • Anaheim

Where does your interest lie, Doctor?

Scientific Section programs will cover a wide spectrum:

☐ Management of airway problems? Acupuncture? Electrical hazards in the operating room? *Anesthesiology.*

☐ Artificial heart valves? Direct Anastomosis to the coronary artery? *Chest Diseases.*

☐ How is high quality medical care measured or monitored in a non-hospital oriented specialty? *Dermatology.*

☐ Medical and surgical management of Strabismus? *Ophthalmology.*

☐ Transfusion therapy? *Pathology.*

☐ Rehabilitation of the stroke patient? *Physical Medicine and Rehabilitation.*

☐ Prevention versus treatment for coronary heart disease? *Preventive Medicine and Public Health.*

☐ Group Psychotherapy in 1973? *Psychiatry.*

Special Conferences explore varied fields:

☐ Melanoma? *7th Annual Cancer Symposium.*

☐ Aviation disasters? Hijacking? *Committees on Disaster and Emergency Medical Care.*

☐ Early intervention on emotional problems? *Committee on Occupational Health.*

More to come in the November issue of **California Medicine.**

In Memoriam

Bielinski, Brunon, Los Angeles. Died July 1, 1972, aged 65. Graduate of the University of Illinois College of Medicine, Chicago, 1939. Licensed in California in 1944. Doctor Bielinski was a member of the Los Angeles County Medical Association.

⁂

Boeck, William Charles, Los Angeles. Died July 27, 1972 in Santa Monica of acute pulmonary congestion and edema, aged 78. Graduate of Harvard Medical School, Boston, 1926. Licensed in California in 1931. Doctor Boeck was a member of the Los Angeles County Medical Association.

⁂

Byars, Jane P., San Francisco. Died August 7, 1972 in San Francisco of diabetes, aged 62. Graduate of University of Texas School of Medicine, Galveston, 1939. Licensed in California in 1947. Doctor Byars was a member of the San Francisco Medical Society.

⁂

Calland, Chad H., San Rafael. Died August 20, 1972 in San Rafael, aged 38. Graduate of University of California School of Medicine, San Francisco, 1959. Licensed in California in 1960. Doctor Calland was an associate member of the Marin Medical Society.

⁂

Chappell, Harry Blake, Dunsmuir. Was killed July 10, 1972 in an automobile accident, aged 41. Graduate of Louisiana State University School of Medicine, New Orleans, 1959. Licensed in California in 1960. Doctor Chappell was a member of the Siskiyou County Medical Society.

⁂

Cheadle, Gerald E., Alameda. Died August 7, 1972 in Alameda of hepatitis, aged 64. Graduate of Western Reserve University School of Medicine, Cleveland, 1939. Licensed in California in 1943. Doctor Cheadle was a member of the Alameda-Contra Costa Medical Association.

⁂

Fedeles, Ladislav Nicholas, Alhambra. Died August 8, 1972 in Arcadia of heart disease, aged 67. Graduate of Lorand Eötvös University of Budapest, 1928. Licensed in California in 1950. Doctor Fedeles was a member of the Los Angeles County Medical Association.

⁂

Gelber, Anita, Los Angeles. Died August 5, 1972 in Los Angeles of carcinoma, aged 77. Graduate of Rush Medical College, Chicago, 1928. Licensed in California in 1932. Doctor Gelber was a member of the Los Angeles County Medical Association.

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Surgical Experience with a Microscopic Transsphenoidal Approach to Pituitary Tumors and Non-Neoplastic Parasellar Conditions

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■ *Improved surgical microscopes and intraoperative radiofluoroscopic television have revived the transsphenoidal approach to pituitary tumors. The transsphenoidal approach offers an alternative to craniotomy, and in certain situations it has distinct advantages. The reported experience includes the common pituitary tumors, hypersecreting microadenomas, cerebrospinal rhinorrhea and parasellar aneurysms. The surgical technique, indications and contraindications, and results in 44 transsphenoidal operations are described.*

A revived interest in transsphenoidal operations has evolved with the introduction of present-day surgical microscopes, brilliant illumination and ocular magnification invalidating earlier objections to the limited visibility provided by this exposure. With the more recent addition of intra-operative televised radiofluoroscopic control, the transsphenoidal approach to certain conditions in and adjacent to the sella turcica has distinct advantages over treatment of the same conditions by craniotomy.

This communication provides a brief historical review of the procedure, describes our transsphenoidal approach to the sellar region and details our experience with transsphenoidal operations in a series of 44 patients.

The Evolution of the Transsphenoidal Approach

The transsphenoidal extracranial approach to the pituitary initiated by Koenig in 1898[1] involved splitting and retracting of the superior maxilla. Shortly thereafter, Giordana suggested a more superior approach with an osteoplastic

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resection of the nose and anterior wall of the frontal sinus, reaching the sphenoid sinus through the ethmoids. In 1907, Schloffer used this method for the first successful removal of a pituitary tumor. Use of Giordana's approach spread rapidly despite the disfigurement entailed, the operative morbidity, and the frequency of infection.

Kanavel[2] observed that the majority of pituitary tumors grew downward, eroding the sellar floor and thereby making the transsphenoidal route preferable to open craniotomy. He abandoned the earlier extensive and multi-staged procedures and advocated elevation of the nose and a direct approach through the sphenoid sinus. Others[3,1] introduced modifications of Kanavel's method, but credit for refining the transsphenoidal approach goes to an otolaryngologist, Oscar Hirsch.[4-7]

Cushing[8] adopted the transsphenoidal procedure and, by 1914, he had performed 74 operations on 68 patients. Equally skillful in approaching the sella turcica from above (by frontal craniotomy) and below (by the transsphenoidal route), Cushing stated, "It is certain that no one method is applicable for all conditions of pituitary tumor and that, for some, no satisfactory procedure has been devised."[9]

Over the next quarter century, intracranial surgery flourished, and because of limited exposure and the risk of meningitis, the transsphenoidal procedure was abandoned by most neurosurgeons. Hirsch continued to use the transsphenoidal approach and, in 1956, reported his results in 413 cases.[5] In the 93 patients treated after the introduction of antibiotics, morbidity dropped to less than two per cent. Other British, French, and Scandinavian surgeons[10,11] adopted this procedure, and in 1961, Hamberger[12] outlined reasons for the returning popularity of the transsphenoidal approach: (1) decreased infection through the use of antibiotics; (2) improved exposure; (3) non-manipulation of optic nerves and chiasm; and (4) craniotomy and its inherent complications were avoided.

Svien[10] investigated the transsphenoidal procedure for excessively enlarged sellas in patients who, in his hands, had done poorly after transfrontal craniotomy. He advocated a return to a more extensive lateral rhinotomy transmaxillary procedure to obtain greater exposure. His criteria for the transsphenoidal operation were: (1) excessively enlarged sella turcica with an aerated sphenoid sinus, (2) absence of suprasellar extension, (3) a secreting pituitary tumor projecting into the sphenoid even without visual defects, and (4) cases in which a large frontal sinus complicated transfrontal craniotomy.

Intra-operative radiofluoroscopic monitoring was introduced by Guiot in 1958. Using fluoroscopic control and a direct midline approach, Hardy[13] indicated the safety of the transsphenoidal removal of pituitary tumors with suprasellar extension and with only minor modifications, we have followed the surgical technique described by Hardy.

Surgical Technique

Frontal and lateral tomograms through the sphenoid sinus and sella turcica define the sellar floor and sphenoidal septa. Patients harboring intrasellar tumors require preoperative pneumoencephalography (with polytomography) and bilateral carotid angiography (Figure 1). In the presence of cerebrospinal rhinorrhea, RISA* cisternography provides crucial localizing information. During the 72 hours preceding operation, the nasal passages are prepared with nose drops made of bacitracin, 500 units per ml, and 0.25 percent phenylephrine hydrochloride (Neosynephrine®). Systemic administration of ampicillin is started 24 hours before operation and continued for five days thereafter.

The patient is placed in a semi-sitting position. After induction of general anesthesia and tracheal intubation, filtered air is introduced by the spinal route for visualization of the third ventricle if earlier studies had indicated suprasellar extension of the tumor. The head is rotated 45° to the right, extended slightly, and held in this position with three-point skull fixation or in a special foam headrest.

The fluoroscopic image intensifier is brought into the operative field and colimated to project a lateral image of the sella turcica on the television monitor. The lower face, nasal cavities, and mouth are cleansed with Phisohex® and benzalkonium chloride (Zephiran®-aqueous); the right lateral thigh is prepared with 1 percent tincture of iodine for possible muscle graft; and the operative field is draped, leaving exposed the nose, upper lip and thigh. The submucosa of the nasal floor and septum and the adjacent

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*Radioactive iodinated human serum albumin.

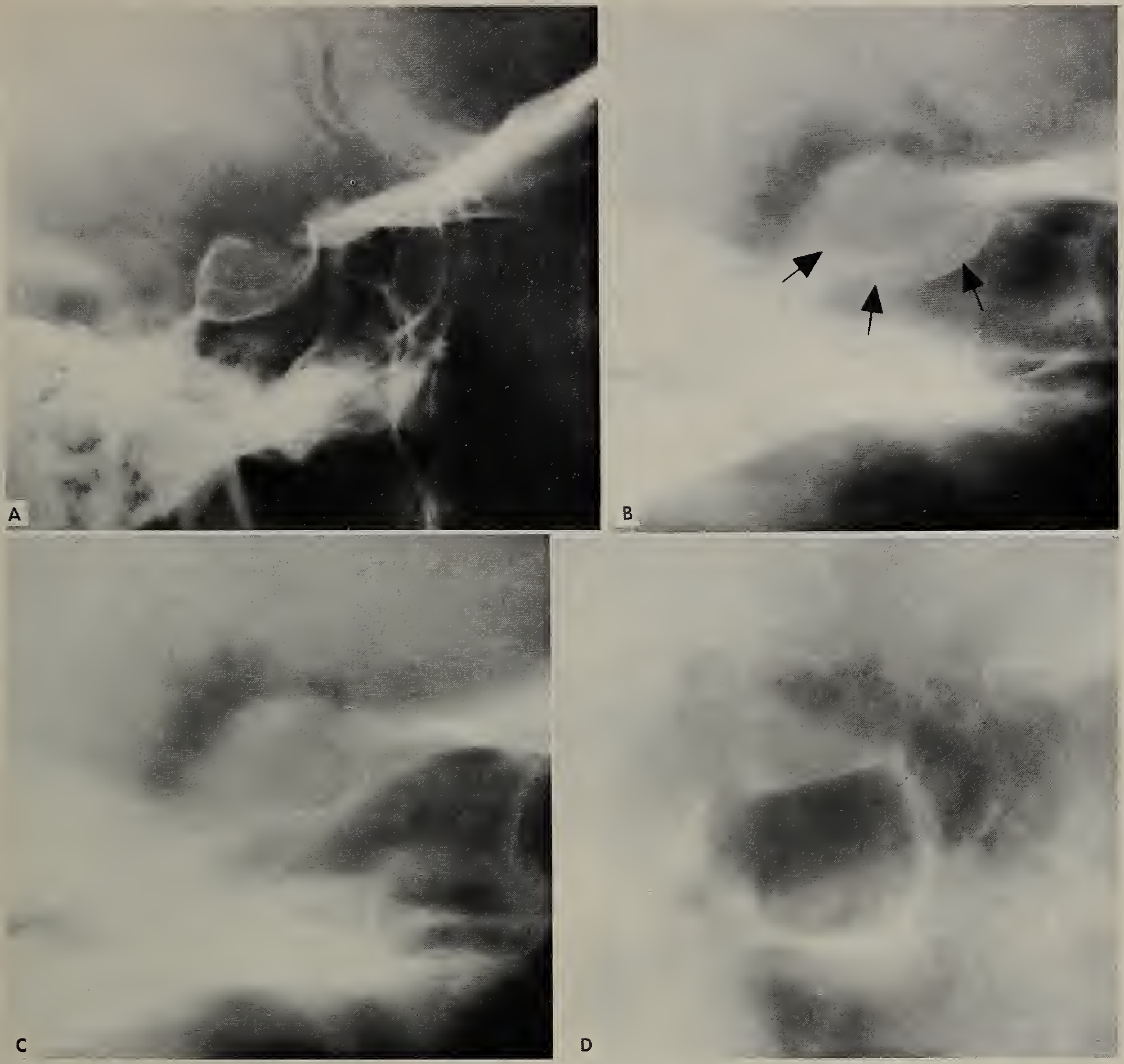

Figure 1.—Typical intrasellar hormone-secreting pituitary adenoma. *A.* Plain film, lateral view of the skull, illustrates the double floor of this sella turcica. *B.* Polytomographic cut, lateral projection to the right of midline, taken during pneumoencephalography shows the deepened right side of the sella with no suprasellar extension of the tumor. Note thinning of the cortical bone (arrows). *C.* Same as *B.* but to the left of midline. The sellar size is within normal limits and the cortical floor is normal. *D.* Polytomographic antereoposterior cut demonstrates the unilateral depression of the sellar floor produced by this right-sided pituitary adenoma.

labial gingiva are infiltrated generously with 0.5 percent xylocaine containing adrenalin 1:2000.

With the upper lip elevated, a transverse incision is made in the labial mucosa 5 mm from the gingival margin. The incision is deepened to expose the maxillary bone between the canine fossae. The upper lip is swept upward with sharp periosteal elevators to expose the piriform aperture, nasal spine, and lower edge of the nasal septum. The nasal spine and the projecting rim of the maxilla are removed to widen and deepen the exposure, and the mucosa is carefully elevated from the nasal septum and floor. Submucosal introduction of a Hardy serrated bivalve speculum exposes the nasal septum and rostral projection of the sphenoid bone. The lower portion of the cartilagenous septum is excised and the vomer is disarticulated to expose the sphenoidal crest. The sphenoid sinus is entered with a high-speed air drill, using the angled Rand handle designed for this purpose. The operating microscope is introduced and the sphenoidal window enlarged to expose the interior of the sphenoid sinus. Removal of the sinus mucosa and sphenoidal septa exposes the anterior sellar wall from the tuberculum sellae to its junction with the floor. The midline is established by reference to the maxillary nasal crest.

Large intrasellar tumors often reduce the sellar floor to mere flakes of thinned bone, while pituitary microadenomas may produce localized bulging and thinning of bone. Depending upon its texture, the presenting sellar bone is removed with the drill, punches or forceps. The dural lining is coagulated with bipolar forceps, and after needle aspiration of the tumor, the dura is opened with a cruciate incision. The intra-sella neoplasm is carefully removed with a variety of malleable spoons and pituitary ronguers, all intrasellar movements being performed under fluoroscopic control. Suprasellar tumor extensions tend to move downward into the excavated sella turcica and this migration can be followed by observing the air-filled third ventricle under closed television fluoroscopy. Any bleeding from within the sella is readily controlled by bipolar coagulation and gentle tamponade.

Pituitary microadenomas are clearly demarcated from the normal anterior pituitary gland. After removing adenomas of moderate size, the flattened yellowish pituitary gland can sometimes be identified on the dorsum sellae. The sellar diaphragm may collapse into the sella and care should be taken to leave it intact while holding it upward to visualize tumor remnants.

If cerebrospinal fluid (CSF) does not appear in the course of the operation, postoperative rhinorrhea is unlikely; a small amount of thrombin-soaked gelatin foam or Surgicel® is placed in the emptied sella. If CSF has entered the operative field, muscle with attached fascia lata is placed in the sella with the fascial surface against the diaphragm. The sellar floor is reconstituted with a piece of nasal septal cartilage. When the sella is massively enlarged, crushed fragments of vomer and maxilla are placed within the evacuated sella to prevent subsequent retraction of the diaphragm and adherent optic chiasm into the remaining cavity. The sphenoid sinus is irrigated with bacitracin, the speculum is withdrawn, and both nasal cavities are packed with vaseline gauze impregnated with bacitracin. The mucous membrane may be closed with catgut sutures, although more recently we have learned that the mucosal edges reapproximate without sutures leaving an almost invisible scar.

After operation the patient is cautioned against nose blowing and sniffing. Nasal packs are removed on the third day. Should cerebrospinal rhinorrhea develop, it is treated by spinal drainage, acetazolamide (Diamox®), moderate fluid restriction and maintenance of a semi-erect position in bed. Ordinarily patients are out of bed on the day after operation.

TABLE 1.—*Indications for Transsphenoidal Operation in 44 Patients*

Pituitary Adenoma	
Non-secreting	
1. visual failure	13
2. normal vision	5
Secreting	
1. somatotrophin	10
2. corticotrophin	4
3. prolactin	3
Craniopharyngioma	4
Cerebrospinal Rhinorrhea	2
Parasellar Aneurysm	3
Total	44

Indications for Operation

During the past four years, 44 patients have undergone transsphenoidal operations, 35 of them for pituitary adenomas. In Table 1 all patients in this series are classified according to operative indication.

Pituitary Adenoma, Non-secreting

The patients in this group harbored non-secreting chromophobe adenomas, and all had one or more clinical expressions of hypopituitarism. Gonadotrophin deficiency, present in every patient, was expressed either as amenorrhea or as loss of libido.

Visual failure constituted the principal complaint and was the operative indication in 13 patients, the majority of whom had been treated earlier by irradiation, craniotomy alone, or craniotomy and postoperative irradiation.

An undiagnosed intrasellar mass with suprasellar involvement of the optic chiasm was the indication for operation in five cases. Preoperatively, four patients were believed to harbor chromophobe adenomas, and one patient, because of extensive sellar erosion and a mass within the sphenoid sinus, was suspected of having a malignant tumor. After partial removal and identification of a chromophobe adenoma, all five patients underwent a course of postoperative irradiation (either Cobalt^{60} or heavy particle).

Pituitary Adenoma, Secreting

Seventeen patients, all adults, had hormone-secreting pituitary adenomas. Clinical syndromes indicated hypersecretion of somatotrophin (growth hormone STH), corticotrophin (ACTH) and prolactin (mammotrophin, PL).

Ten patients had clinical features and laboratory evidence of acromegaly due to excessive STH. Two patients had undergone craniotomy followed by postoperative radiotherapy in the past, and both tumors extended above the sella turcica. One patient, previously untreated, had a large tumor that had deformed the optic chiasm without affecting vision. Because of suprasellar extension, this tumor was not suited for cryohypophysectomy, and transsphenoidal removal was selected rather than craniotomy. A fourth patient, an acromegalic, had a large mass within the sphenoid sinus and removal of the extrasellar component established the diagnosis of an eosinophilic adenoma. Following operation, the remaining tumor was treated by heavy particle irradiation. The remaining six patients presented with previously untreated clinically active acromegaly and an enlarged sella turcica. In two of these, craniotomy would have been difficult because of pathologically thickened frontal bones.

Four patients had ACTH-secreting pituitary adenomas. All four had been treated for Cushing's syndrome by bilateral adrenalectomy four to 15 years earlier. After adrenalectomy, these patients became hyperpigmented and had greatly elevated values for plasma ACTH. All were suspected of harboring ACTH-secreting pituitary adenomas (the post-adrenalectomy syndrome described by Nelson[14]), and serial skull films had been compared in order to detect the earliest indication of sellar enlargement. Up to the time of transsphenoidal operation, measurements of all four sellas remained within normal limits. However, in three instances retrospective examination of sequential films revealed an increase in the overall dimensions of the sella, and in all other cases tomograms of the sella demonstrated asymmetric bulging of the anterior sellar floor. The slight sellar changes produced by small pituitary adenomas (microadenomas) will be the subject of a separate report.

One patient with Nelson's syndrome presented with pituitary apoplexy: sudden onset of headache, nuchal rigidity and involvement of all nerves passing through the right cavernous sinus caused by bleeding into the adenoma. Transsphenoidal removal of the hemorrhagic adenomas was done as an emergency procedure. The other three patients in this group underwent elective removal of microadenomas.

Three female patients sought medical attention because of galactorrhea and amenorrhea secondary to pituitary adenomas (Forbes-Albright syndrome). All three were presumed to be harboring prolactin-secreting adenomas, although this was confirmed preoperatively by serum PL levels in only one patient. In one patient the adenoma had invaded the orbit and cavernous sinus, and removal of the intrasellar component of an histologically benign adenoma was followed by irradiation. The other two patients harbored microadenomas, and transsphenoidal operation was undertaken on the basis of localized thinning and downward bulging of the anterior sellar floor in association with the endocrine abnormality.

Craniopharyngioma

Four children underwent transsphenoidal operation for craniopharyngiomas. One child had had multiple craniotomies and in the most recent procedure a large recurrent cyst had been drained through a stereotaxically placed transsphenoidal opening in the intrasellar cyst wall. Six months later, the 4 mm opening closed and the cyst refilled. At that time the intrasellar cyst wall was exposed and a window 1.5 cm in diameter was made between it and the sphenoid sinus and nasopharynx. The second child was referred when intrasellar calcification was discovered during the course of an investigation for small stature. The sella was not enlarged and an air contrast study revealed only a 5 mm suprasellar nodule. A cystic craniopharyngioma was removed intact by the transsphenoidal approach. The third child was referred when skull films obtained for minor head trauma disclosed asymptomatic sellar enlargement although his stature was small for his age. Tomography revealed no intrasellar calcification and, except for a minute nodule projecting beneath but not touching the optic chiasm, the tumor was confined to the expanded sella. Among craniopharyngiomas discovered in childhood, the frequency of radiographic calcification approaches 100 percent, and on this basis the preoperative diagnosis was pituitary adenoma. At operation, a soft, non-cystic tumor was removed, while sparing the uninvolved pituitary gland that was identified lying against the dorsum sellae. Microscopic examination of the tumor revealed an atypical papillary craniopharyngioma and the child is now receiving radiotherapy. The fourth patient, aged 16, was treated by craniotomy and twice thereafter with transsphenoidal drainage. His vision recovered to normal levels after each procedure.

Cerebrospinal Rhinorrhea

Two women were referred by neurosurgical colleagues when post-traumatic cerebrospinal rhinorrhea recurred after intracranial exploration. In each case the earlier craniotomy had not disclosed a definite fistula suspected in the cribiform plate of the ethmoid sinus. In both cases a fistula between the sella turcica and the sphenoid sinus was confirmed and closed by the transsphenoidal approach.

Parasellar Aneurysms

Three patients were referred because of progressive blindness secondary to giant parasellar aneurysms. Because of their size and configuration, these three aneurysms were unsuited for intracranial clipping and we elected to treat them by electrothrombosis, using a technique developed by one of us (Y.H.). A transsphenoidal approach to the tuberculum sellae allowed the construction of coordinates appropriate for introducing needles and wires into each aneurysm.

Complications (Table 2)

The only death occurred in a patient who suddenly died following an apparently uneventful recovery from electrothrombosis of a large suprasellar aneurysm. Her death, due to pulmonary embolism, had no direct relationship to the transsphenoidal approach.

Six patients developed transient postoperative cerebrospinal rhinorrhea. The rhinorrhea ceased after one or more lumbar punctures, in three cases supplemented by Diamox® and moderate restriction of fluid intake. One child removed his nasal packing in the recovery room, and persisting rhinorrhea required insertion of a larger muscle pack four days later.

TABLE 2.—***Complications after Transsphenoidal Operations***

Complications	
Postoperative rhinorrhea, transient	6
Postoperative rhinorrhea, requiring operation	1
Visual loss requiring reoperation	1*
Hematoma at muscle donor site	1
Deaths	1†

*Full recovery in 48 hours.
†Parasellar aneurysm; death unrelated to transsphenoidal procedure.

One patient, whose vision was impaired before operation, became blind eight hours after transsphenoidal removal of a partially cystic chromophobe adenoma. He was taken immediately to the operating room and the sella was quickly re-exposed. A large nodule of tumor attached to the tuberculum sellae had been missed at the original operation; postoperatively, because of infarction and hemorrhage related to surgical penetration, it had expanded to compress the optic chiasm. Vision returned to the preoperative pattern within 48 hours.

One patient required drainage of a hematoma that developed at the muscle donor site.

Results

Pituitary Tumors, Non-secreting

Among the 13 patients with impaired vision, only one (described above) had postoperative complication. All 13 left the hospital with vision either unchanged or improved. The vision of one or both eyes has improved in 11 patients, one patient has been lost to followup, and one was operated upon less than one month ago.

The five patients with normal vision had an uneventful recovery. Their tumors were subsequently irradiated.

Pituitary Tumors, Secreting

The ten acromegalic patients made satisfactory recovery although one developed a hematoma in the thigh. Clinical expressions of hypersomatotrophism have improved in six patients. This was confirmed in two patients by measurement of serum somatotrophic hormone (STH), and the other patients reside in distant parts of the United States. Three patients have recently completed a course of heavy particle irradiation. Although three patients had suprasellar masses, none had impaired vision either before or after operation.

Depigmentation and a rapid fall in plasma ACTH values characterized the postoperative courses of three patients with Nelson's syndrome. The fourth patient, treated less than one month ago, has not undergone postoperative endocrine evaluation. Normal menstruation resumed in the one amenorrheic patient with a microadenoma. The significance of elevated ACTH persisting in three patients is unknown. The cavernous sinus syndrome has not resolved completely in the patient with pituitary apoplexy, but increasingly severe pain in the trigeminal distribution suggests neoplastic invasion of the trigeminal ganglion.

All three patients with the Forbes-Albright syndrome had immediate cessation of galactorrhea and early resumption of menstrual periods. The patient whose tumor had invaded extrasellar structures has completed a course of radiotherapy. Her partial oculomotor palsy and proptosis improved immediately after operation and almost completely resolved during radiotherapy. Postoperative irradiation was done in one patient with microadenoma and was not advised in the other patient because gross total removal of the adenoma was accomplished.

Craniopharyngioma

One patient who had undergone multiple surgical procedures and irradiation for a repeatedly recurrent cyst has remained symptom-free in the two years since a large window was created between the cyst and the sphenoid sinus. Successful drainage was also achieved in another patient by this technique.

The patient whose cystic intrasellar tumor was totally removed is doing well in school and engages in active sports. Complete panhypopituitarism requires replacement therapy, including growth hormone. The boy who harbored the atypical solid craniopharyngioma is receiving radiotherapy. We anticipate normal pituitary function, and the critical laboratory tests will be performed after he completes the course of irradiation.

Cerebrospinal Rhinorrhea

Both patients recovered rapidly following operative obliteration of sphenoid fistulas, and they have remained well for periods of three months and six months respectively.

Parasellar Aneurysms

A detailed account of the three patients undergoing transsphenoidal electrothrombosis will be included in a separate report. In the two surviving patients, aneurysmal thrombosis arrested visual deterioration, and in one of them vision has improved slightly.

Discussion

For the majority of non-secreting pituitary adenomas with suprasellar extension and optic chiasmal compression, the transsphenoidal approach provides an alternative to craniotomy. In the usual adenoma with smooth dome-like expansion out of an enlarged sella, transsphenoidal removal will achieve end results comparable to those obtained by craniotomy, but with the advantages of less risk and lower morbidity. We advise postoperative irradiation unless the tumor proves to be a cyst devoid of identifiable adenoma. When preoperative air contrast studies indicate either markedly eccentric extrasellar growth or waist-like constriction of the tumor where it extends through the sellar diaphragm, transsphenoidal removal is contraindicated.

The transsphenoidal approach appears to be the procedure of choice in the following situations:

- *The enlarged sella turcica discovered either incidentally or in the course of endocrine evaluation (for example, amenorrhea) or workup for headache.* After cerebral angiography and air contrast study have excluded an aneurysm, a suprasellar mass, hydrocephalus, and an "empty sella," in the past the majority of patients in this category have been referred for radiotherapy with the presumptive diagnosis of a non-functioning pituitary adenoma, and the rest have been followed without treatment.

We advocate transsphenoidal exploration for two reasons. First, the responsible lesion may be a non-neoplastic cyst or a largely cystic adenoma, both responding poorly or not at all to irradiation. Second, if the intrasellar mass proves to be a solid pituitary adenoma, operative removal followed by irradiation offers a greater chance of cure than irradiation alone. This latter statement is based upon general experience with animal tumor systems in which the probability of radiocurability is inversely related to tumor size.

- *Pituitary tumors recurring after craniotomy or irradiation or both.* Following unsuccessful initial treatment, transsphenoidal removal offers an advantage over craniotomy, either primary or secondary. Many patients hesitate to submit to a second craniotomy, and the tumor recurring after (or unaffected by) irradiation is often cystic.

- *Intrasellar tumors with a major component occupying the sphenoid sinus.* Pituitary tumors that penetrate the sellar floor to invade the sphenoid sinus usually exhibit this pattern of growth because the sellar diaphragm is unyielding. These tumors are better managed from below than from above.

- *Pituitary apoplexy.* Sudden hemorrhage and infarction of a pituitary adenoma, occurring either spontaneously or during the course of irradiation, represents a medical and surgical emergency.[15] Rapid expansion of the mass characteristically causes visual loss, impairment of cranial nerves in the cavernous sinus, acute hypopituitarism manifested by adrenal insufficiency, and subarachnoid hemorrhage. After correcting life-threatening metabolic derangements, the surgeon must relieve pressure on the critical structures. The speed and associated low morbidity of transsphenoidal decompression favor this approach in these typically ill patients.

- *Failing vision in elderly and debilitated patients.* Because the transsphenoidal approach involves a shorter period of general anesthesia and avoids certain hazards inherent to craniotomy, it can be advised for patients who are poor surgical risks. In this circumstance, an operation with a limited objective—decompression of the optic chiasm—can be performed by the transsphenoidal approach in view of the procedure's speed and low morbidity.

Still undefined is the role of transsphenoidal removal in the treatment of functioning pituitary adenomas. For the STH-producing adenoma associated with gigantism and acromegaly, the primary treatment of choice has been either heavy particle irradiation or stereotaxic cryohypophysectomy. Transsphenoidal removal provides an alternative to craniotomy in the management of tumors with symmetrical suprasellar extension and tumors recurring after irradiation and cryosurgery.

The recent surgical verification of hormone-secreting pituitary microadenomas introduces a new concept into clinical endocrinology. Some functioning microadenomas eventually erode the sella and produce signs of an enlarging intrasellar tumor. Other microadenomas may continue to secrete their hormonal product for extended periods of time. Using polytomography, we have identified subtle sellar changes produced by tumors less than 1 cm in diameter. To date, we have not removed a microadenoma from a sella that lacked some structural abnormality.

ACTH-secreting microadenomas may prove to be a common cause of Cushing's syndrome; Hardy has removed such a microadenoma.[11] Present evidence strongly suggests that a microadenoma underlies Nelson's syndrome, and it is reasonable to assume that the microadenoma existed before adrenalectomy.

Our experience indicates that prolactin-secreting microadenomas can produce galactorrhea and amenorrhea (Forbes-Albright syndrome).[16] Del Castillo described amenorrhea and galactorrhea in nulliparous non-gravidas without apparent cause (Agronz-del Castillo syndrome). These same symptoms occurring in association with sellar enlargement (presumptive evidence of a pituitary tumor) constitute the Forbes-Albright syndrome, the obvious differentiating feature being the absence or presence of a *recognized* pituitary tumor. We suggest that a significant number of patients carrying the diagnosis of Agronz-del Castillo syndrome may harbor microadenomas. Hardy[11] has removed a microadenoma from a patient with thyrotoxic exophthalmus and a high level of long-acting thyroid factor. Other endocrinopathies may have a similar basis.

Our experience with microadenomas supports the observations of Hardy.[15] He found that microadenomas occupy the rostral surface of the anterior pituitary gland and consequently lie superficially against the anterior sellar floor. He further observed that microadenomas have a sharp line of demarcation from the normal gland. If this anatomical arrangement proves to be a consistent finding, microadenomas are ideally suited to operative removal by the transnasal-transsphenoidal approach with the decided advantage of protecting and sparing the normal pituitary gland and its hypothalamic connections.

The transsphenoidal approach offers an alternative to intracranial removal of strictly intrasellar craniopharyngiomas. If the intrasellar tumor adjoins a well-pneumatized sphenoid sinus and if preoperative air contrast study indicates short optic nerves, the transsphenoidal operation has advantages over craniotomy. The transsphenoidal approach also provides a safe and simple means of draining cystic craniopharyngiomas. If a part of the cyst wall lies within the sella, permanent drainage can be established by creating a large opening between the cyst and the sphenoid sinus.

Cerebrospinal rhinorrhea seldom originates from a congenital fistulous opening into the sphenoid sinus, and excepting those that occur with pituitary tumors, the majority of fistulas follow trauma. After diagnostic procedures have established the presence of a sphenoid fistula, transsphenoidal repair is the procedure of choice.

In a growing experience with electrothrombosis, the utilization of several different surgical approaches has increased our ability to deal with a variety of intracranial aneurysms. The transsphenoidal exposure of large parasellar aneurysms has two principal advantages: first, wires and needles can be introduced into the aneurysm without the deep retraction required during intracranial exposure; and secondly, the transsphenoidal approach is well-tolerated even by seriously ill patients. Our favorable experience with the three cases herein reported encourages its future use.

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ALCOHOL TO DISINFECT THE HANDS

Can you really disinfect hands with alcohol?

I know from skin studies by the thousands that the application of a little acidified alcohol will remove all the surface bacteria by the time it evaporates from the hands. It is the single most effective way of disinfecting hands. I can provide a ton of data to prove this point. If you add some hexachlorophene, it's even more effective. . . . Isopropyl alcohol or ethyl alcohol (70 percent) are enormously effective. They're kind to the skin and they do stop the digital and manual transmission of contamination much better, much more effectively than what we call handwashing.

What about drying the hands afterward?

I like to see the user just let the alcohol evaporate, which it does very quickly.

—Carl W. Walter, m.d., Boston
Extracted from *Audio-Digest Surgery*, Vol. 17, No. 9, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

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Nov 1972

Aerotitis in Air Travel

C. Richard Wolf, m.d., *Berkeley*

■ *In the years 1964-1969, 2,015 cases of aerotitis were reported as an occupational disease in California. Most of the cases were in women flight crew members on commercial airlines (women predominate in such crews). Cases were also reported in passengers. Upper respiratory infection frequently appeared to be a predisposing event.*

The pressure in the middle ear normally adjusts to external air pressure changes through the eustachian tube. Failure of this pressure equalization initiates a disease process termed aerotitis by Armstrong.[1] The jet aircraft used in present-day air travel maintain cabin pressure at sea level during flights up to 20,000 feet. On longer flights at altitudes up to 40,000 feet, the cabin pressure would be approximately 6,000 feet. This is enough difference to cause aerotitis. The cause of aerotitis is inadequate ventilation of the middle ear during descent from flight. This may be due to failure of the eustachian tube to open spontaneously, and then inability to open the eustachian tube by deliberate effort.

Edema and reactions of the mucosa secondary to allergy or upper respiratory infections are usually the cause of this blockage of the eustachian tube. The orifice of the eustachian tube then acts as a check valve, letting no air pass into the middle ear if there is sufficient swelling at its opening into the oropharynx. When this occurs during descent from flight, the middle ear has a pressure relatively negative to that of atmospheric pressure. This negative pressure produces a sterile exudate in the middle ear. The exudate and the consequent trauma to the immediate surrounding tissues in the tympanic cavity produce a pathologic state similar to that of serous otitis media.

Diagnosis

The diagnosis of aerotitis requires the following: History of exposure to a situation in which changes in barometric pressure occurred, and physical examination disclosing signs which closely resemble the various stages of otitis media. In the early stages, there will be simply retraction of the drum.

Treatment

The treatment of aerotitis is the same as for otitis media. This includes administration of decongestants and antibiotics. Careful attention during follow-up visits should be directed at watching for recurrence of chronic serous otitis. Further exposure to changes in air pressure should be avoided during the course of the disease. If improvement is not immediate, an ear, nose and throat specialist should be consulted, as myringotomy may be necessary.

Complications

Complications of aerotitis result from infection which rapidly leads to otitis media that is no different than the otitis media of any other cause. Following this, the course of the disease can go

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Reprint requests to: C. R. Wolf, M.D., Medical Officer, Bureau of Occupational Health and Environmental Epidemiology, State Department of Public Health, 2151 Berkeley Way, Berkeley, Ca. 94704.

on to chronic infection or can set up a chronic serous otitis, which has been described by Vogel[2] as a frequently overlooked cause of deafness. A search of the literature discloses no reports specifically referring to hearing loss as a result of aerotitis in adults. However, Olmsted[3] described cases of hearing loss in children as a result of middle ear infection and Beauregard[4] discussed positional otitis media.

Prevention

Prevention of aerotitis has been basically approached by limiting the speed of descent of aircraft or by controlling the pressurization in aircraft to the point that the pressures between the middle ear and the environment can equalize without blockage. When swelling of tissues owing to upper respiratory infection or allergic reaction prevents equalization by impeding the free exchange of air through the eustachian tube, there are several measures that will help. Collip[5] studied the use of nasal decongestants in children with otitis media as a therapeutic measure. In commercial air travel, decongestants serve as a means of assisting in equalizing pressure to prevent aerotitis. Swallowing is the standard measure suggested; if this fails, a variation of the Valsalva maneuver is suggested. This maneuver in itself is not without some risk, as Watson[6] described a relationship of the Valsalva maneuver to chronic recurrent otitis media. In this variation of the Valsalva maneuver, air is forced into the middle ear by forced expiration against a tightly closed mouth and with nose pinched closed. Nasal vasoconstricting agents should be made available to both crew and passengers. Crew members with upper respiratory infections should be grounded. Sufficient sick leave should be granted new employees to insure that they not fly when they have a cold. Passengers with upper respiratory infections should be advised of the risk.[7] Babies should be awakened and set upright before descent.

Clinical Data

The clinical data contained herein was taken from descriptions of the cases of aerotitis reported by physicians in the State of California to the Division of Labor Statistics on the *Doctor's First Report of Work Injury*. Problems of underreporting and, on occasion, inaccurate reporting exist and have been studied and reported.[8,9] On the whole, however, these reports make up a great potential source of information about the relative importance of various hazardous conditions not otherwise reported.

TABLE 1.—***Reports of Aerotitis, California, 1964-1969***

Year	
1964	170
1965	199
1966	220
1967	309
1968	529
1969	588
Total	2,015

Source: State of California, Division of Labor Statistics and Research, *Doctor's First Report of Work Injury*. Statistics compiled by State of California, Department of Public Health.

TABLE 2.—***Reports of Aerotitis by Month of Injury, California, 1964-1969***

Month of Injury	*Number*	*Percent[1] (adjusted)*
Total	2,015	100.0
January	232	11.4
February	156	8.5
March	192	9.4
April	162	8.2
May	165	8.1
June	154	7.8
July	110	5.1
August	141	6.9
September	151	7.7
October	147	7.2
November	174	8.8
December	215	10.6
Not Reported	16	—

Note: Percents may not add to totals because of rounding.
[1] Adjusted for number of days per month.
For source, see Table 1.

Each year in California, physicians report some 30,000 cases of occupational disease. This total figure varies a few thousand from year to year, reflecting the exclusion of specific diseases from reporting categories. Aerotitis has consistently been tabulated and successive years are therefore comparable, as shown in Table 1. The total number of cases reported has been increasing steadily. Our investigations have found no reason other than the increase in commercial air travel. From the reports it appeared that allergic reaction and upper respiratory infections were prime causes of aerotitis.

Table 2 compares the number of reports of aerotitis received by month of injury. This table clearly indicates a trend toward increasing numbers of aerotitis occurring during winter months.

Table 3 shows that of the 2,015 industrial cases

TABLE 3.—*Reports of Aerotitis, by Industry, California, 1964-1969*

Year	*Industry* *Airlines*		*Other Industries*		
1964	132		38		
1965	164		35		
1966	181		39		
1967	266		43		
1968	488		41		
1969	555		33		
6 year TOTAL	1,786	+	229	=	2,015
Percent	88.6%	+	11.4%	=	100%

TABLE 4.—*Reports of Aerotitis by Sex, California, 1967*

	Employees of Scheduled Airlines	*Passengers*	*Total Reports*
Men	27 (10%)	43 (100%)	70 (23%)
Women	239 (90%)	0 (0%)	239 (77%)
	266	43	309

of aerotitis reported in the period 1964-1969, 1,786 occurred in airline personnel. Most of the 229 cases in employees of other industries generally occurred in passengers flying on commercial aviation in the course of their regular work. The increase in number of cases of aerotitis throughout the airline industry accompanied expansion in commercial air travel for the same period. Seventy-nine percent of the patients in the industrial cases were women. Far more men than women travel on airplanes in connection with their employment and are thus covered by workmen's compensation. On the other hand women predominate as air-crew employees. Reports summarized in Table 4 reflect this difference in exposed populations. Thus in 90 percent of the 266 cases reported in employees the patients were women. All of the 43 cases reported in passengers were in men.

When an employee's duties involve exposure to air pressure changes, this disease condition requires considerable time lost from work. In one study group, 71 percent of 1,426 patients lost one to fourteen days from work. There is no clear-cut relationship between the number of scheduled flights by an airline and the number of reports filed by its employees. For example, the airline that had the most take-offs and landings for the study period reported no cases of aerotitis.

Reported cases varied widely from airline to airline, probably reflecting personnel practices regarding sick leave, since our investigations revealed no significant exposure variables that would account for the variance. This was presumed to be a reflection of individual airlines' personnel policies. The cases of aerotitis were treated by many physicians, from all over California, with a treatment pattern consisting usually of antihistamines, decongestants and antibiotics.

An analysis of 309 cases disclosed the following: The right ear was involved as often as the left, and both ears about as often as either individually. Although, usually treated on the day of onset, frequently many days elapsed before the first visit to a physician. Myringotomy was reported in ten instances, but there may have been more that were not reported. Audiograms were done in nine cases but the nature of our reporting system, which discloses only the patient's first visit to the physician, does not permit any conclusions as to resultant hearing loss.

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Hydatid Disease Is Endemic in California

CALVIN W. SCHWABE, D.V.M., SC.D., ROGER RUPPANNER, D.V.M., M.P.V.M., CARL W. MILLER, D.V.M., M.P.V.M., ROBERT E. FONTAINE, A.B., *Davis*, AND IRVING G. KAGAN, PH.D., *Atlanta, Georgia*

■ *Hydatid disease, a parasitic infection of global importance and a condition for which there is no known medical treatment, is established endemically in the Central Valley of California. Only further study will reveal whether or not the infection is now spreading or intensifying or is remaining fairly stable at a relatively low level of endemicity. California physicians should be aware of its presence and the fact that in most sheep-raising areas of the world it constitutes a problem of major medical and public health importance.*

Although a number of national or regional programs for hydatid disease control have been undertaken, clear progress has been evident only in Iceland, in New Zealand and in the Australian state of Tasmania.[2,4,5]

UNTIL RECENTLY, LITTLE WAS KNOWN about hydatid disease in the contiguous United States except that it existed, although presumably at a very low level. Evidence for this was its sporadic diagnosis over the years in about 60 persons who apparently had never traveled outside this country, Department of Agriculture veterinary postmortem summaries from slaughterhouses indicating occasional condemnations of cattle livers because of hydatid cysts, two surveys reporting infections in slaughtered swine in Mississippi, and the diagnosis since 1892 of Echinococcus tapeworm infections in 15 dogs, mostly in the southeastern United States, and in several timber wolves in Minnesota.[1] Hydatid cyst infections had not been reported in sheep in the United States, although that species is the most important intermediate host for Echinococcus granulosus in endemic areas of Latin America, Australasia, the Mediterranean littoral, the Middle East and Central Asia.[2-5]

Present Knowledge of Hydatid Infection in California

Until our studies, which began in 1967, published knowledge of the occurrence of hydatid disease in California consisted of two case reports from 1951 and 1957 describing operations on a 14-year-old boy and a 27-year-old man, neither of whom apparently had been outside of this state.[6,7] Since then, however, we and our associates have described an area for E. granulosus transmission in the Central Valley of Cali-

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These studies were supported in part by research grant AI-07857 from the National Institutes of Health and a grant from the World Health Organization.

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fornia extending from Tehama County in the north to Kern County in the south.[1,8,11] These investigations began with a prevalence survey in 1967 and 1968 which disclosed hydatid cysts in 4.8 percent of a series of 22,720 adult sheep submitted for slaughter in California. Several lots of infected sheep were traceable to their ranches of origin, where the complete dog-sheep cycle of the parasite was demonstrated for the first time in the United States; and associated human infections were found.[1,8] Two of these human cases were definitely autochthonous to California. Further research revealed relatively common infections both in coyotes and deer,[9,10,12] particularly in the northern part of the Sacramento Valley.

Subsequently, retrospective epidemiologic studies of the records of 82 California hospitals (located from the Bay Area and Sacramento south) for 1960-69,[11] and for a number of years before that for two hospitals in San Francisco and Fresno,[13] yielded information on 97 human cases of hydatid disease, at least 14 of them definitely acquired in California. Most of the patients had been associated with the sheep industry of California, and a number of them were of Basque extraction.

A further extension of these epidemiological studies to 44 hospitals in California north of San Francisco and Sacramento[14] yielded data on five additional infections, none of which could be proven autochthonous.* Studies are now in progress to determine the extent to which a sylvatic cycle of infection exists, and to define the possible relationship of the Basque sub-culture in California to the history, distribution and maintenance of hydatid infection in this state.

Diagnosis of Hydatid Infection

Relatively few American physicians have had experience in the diagnosis of hydatid disease. In man roughly 65 percent of hydatid cysts occur in the liver, 25 percent in the lungs and the remainder in other organs. Hydatid infection should be considered whenever a space-occupying mass is revealed in the thoracic or abdominal cavities. For this purpose, the liver scan is of definite value, and chest radiographs which show a sharply demarked, spherical or nearly spherical shadow are particularly suggestive.[11] An elevated blood eosinophile count is not a consistent finding in hydatid disease, but if present supports a diagnosis. The patient's history will frequently indicate present or past association with sheep or dogs. Paracentesis is definitely contra-indicated because of danger of cyst rupture or leakage with the possibility of anaphylaxis or secondary cystic sequellae.

The Casoni intradermal test should be performed if possible in all suspected cases.[1,15] This test has a sensitivity of about 90 percent and most infected persons show an immediate-type wheal of over 1 sq cm in area with a negative control within 45 minutes.** As the specificity of this test, as routinely performed, is not particularly high, skin test-positive patients, and preferably all suspected patients, should also be subjected to the indirect hemagglutination test. This test is available in the United States only at the National Center for Disease Control. Arrangements to have it done may be made through the laboratories of the California State Department of Public Health. A diagnosis is confirmed by the finding of typical hooklets, protoscolices or cystic membrane on pathological examination of the surgical specimen.

Epidemiological Follow-up

Although hydatid disease is not now reportable in California, epidemiological follow-up should be done in all cases for the following reasons: (1) Other persons in the patient's family or close associates may have been at similar risk of exposure to the same infected dog, (2) an infected dog or dogs may still be present in the patient's household,* (3) a focus of transmission involving farm animals may be disclosed and steps taken for its control. A fourth and obvious purpose of such a follow-up is its value for the education of the patient and his family. For these reasons, reporting of cases in humans to the Veterinary Public Health Section of the California State Department of Public Health is urged.

The nature of the patient follow-up required is indicated in the following four examples, the first three of which are previously unpublished accounts of investigations on autochthonous cases revealed in our studies of California hospital records.[11]

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*However, one woman patient in this group was born in Colorado but raised on a farm in the Central Valley of California, where she had had numerous contacts with dogs. She very probably acquired the infection in this state.

**Casoni skin test antigen is not obtainable commercially in the United States. Small quantities are sometimes available from the senior author's laboratory or from the National Center for Disease Control, Atlanta, Georgia.

*In consulting the family's veterinarian it is important for the physician to know that most American veterinarians are as yet unfamiliar with the procedure for the diagnosis of E. granulosus infections in dogs. Since the eggs of this parasite are identical to those of several other commonly occurring taeniid tapeworms of the dog (none of them of human health importance), none of the usual stool examination techniques are of value in diagnosis. The somewhat laborious diagnostic procedure which is required is fully described in one of our earlier reports.[8]

Case 1.

Admission: In March 1969 a seven-year-old boy, the son of a farmhand, was admitted to the hospital with a tentative diagnosis of echinococcal cyst. Three weeks earlier he had been struck in the chest by a shoe thrown by a brother. The resulting pain prompted a medical examination, and a radiograph showed density low in the right side of the chest. Fluid was withdrawn and "bodies resembling echinococcal scolices were found." No serologic or skin tests were mentioned in the records.

Diagnosis: One day following admission a lower lobe lobectomy was performed on the right lung. The pathology report confirmed the diagnosis of an E. granulosus cyst.

Follow-up: In July 1970 we visited the home of the patient. He had been born in Selma, California, in 1961, had lived there all his life and had not been outside the San Joaquin Valley except for an occasional few days' vacation at Hollister, California. While at Hollister he had had no contact with livestock. Also he had had no known association with livestock in the Selma area, except during one school field trip to the Fresno zoo. He had had numerous contacts with dogs, however. He brings stray dogs home, where they are sometimes allowed to remain for extended periods. According to the patient's teacher, he has a great deal of freedom after school and spends many hours roaming around town. He probably thus has had many opportunities for contact with dogs.

The patient's mother is a Mexican woman who moved from El Paso, Texas, to the San Joaquin Valley in 1935. Except for a two-month period in Mountain View, California, shortly after coming from Texas, she has lived continuously in the San Joaquin Valley. She has 12 living children, all of whom were born in the valley and still live in the central part of the valley, including six who remain at home. Several of the patient's brothers and sisters sometimes work as farm laborers. At the time of our visit the family had two dogs, one they had had for several months, the other for only two weeks. The chronology of events in this case indicated that neither dog could have been the source of infection.

Blood specimens were drawn* from eight members of this family for serologic testing. The results of indirect hemagglutination tests performed at the National Center for Disease Control (CDC), Atlanta, included two borderline titers and prompted us to obtain a second series of serum specimens about nine months after the first sample, and to request chest radiographs on two sisters of the patient, one 8 years old, the other 13. The radiology reports indicated normal chests. None of the serum specimens showed a diagnostic titer nor had any of the titers changed significantly over the nine-month period.

Although the source of this infection was not found, it was clearly autochthonous to California.

Case 2.

Admission: The patient, a girl two and a half years old, was admitted to the hospital in August 1963 with a history of coughing for 24 hours. On the day of admission a chest radiograph revealed a mass in the upper lobe of the left lung.

Diagnosis: On the third day a Casoni skin test was performed and found to be positive (erythema 2 cm in diameter, no induration). On the tenth day exploratory thoracotomy led to the removal of two cysts from the left upper lung lobe. Pathological examination confirmed the diagnosis.

Follow-up: In July 1970 we visited the home of the patient, who was then 9 years old, to obtain information about her residential history and past association with dogs or livestock. Her father was a farm laborer. The family had moved many times, but all of the moves had been in the area of south-central Fresno County or northwestern Tulare County in the San Joaquin Valley.

The patient had been born in the Fresno General Hospital in 1961. At that time the family was living in Orange Cove, California. When she was a few months old the family lived with her father's father on a citrus ranch southeast of Orange Cove. There were a few sheep and goats at his home on the ranch, and the patient's father recalled that goats occasionally came into the house. After a few months on this ranch the family returned to Orange Cove and lived at two addresses in town. They then moved to a rural address east of Reedley, California. During that entire period the family often visited the grandfather on the ranch.

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*The cooperation of Dr. Edward Kitts, Selma, California is gratefully acknowledged.

The patient thus could have been exposed to hydatid infection at several locations, even at home. Her father occasionally purchased goats or sheep while she was a baby and these animals were slaughtered at home and the viscera fed to the family's dogs. At the time of our visit the father had two young dogs which he intended to train for hunting.

We had blood specimens drawn* from all five members of the family. Indirect hemagglutination test results from the CDC led us to believe that the patient's father and one of her sisters might possibly be infected. In May 1971 we obtained a second series of blood specimens and arranged for a complete medical examination on the father and the sister in question plus chest radiographs on all members of the family. None of the serological titers were considered diagnostic at that time and the medical examinations revealed no abnormalities. The radiologic reports indicated "negative chest," with the exception of the patient's, which was reported as showing "some scoliosis of the spine and an abnormal rib 4th posterior on the left."

We could not identify the source of the patient's infection but concluded from her residential history that she had acquired it within California.

Case 3.

Admission: A 34-year-old woman was admitted to the hospital in April 1966 because of increasing pain of long standing in the epigastrium. On the first day of her stay in the hospital a radiologic examination disclosed two large densities in the liver, one on the right and one on the left. On the third day the following operations were carried out: cholecystectomy and evacuation of a hydatid cyst in the left side of the liver (the radiographic density on the left). Records indicated that the less accessible suspected cyst in the right side of the liver was not evacuated or excised during this stay at the hospital, nor were there any later admissions. It was left undisturbed, and the patient is aware that this was so.

Diagnosis: There is no mention of a skin test nor serologic tests for echinococcosis in this patient's records. However, microscopic examination of the contents of the removed cyst revealed protoscolices and hooklets characteristic of Echinococcus.

Follow-up: We carried out investigation in 1970. The patient had been born in Porterville, Tulare County, California, and was currently employed as a waitress. She had never been outside the United States, and had only been outside California one time, when she traveled briefly to Reno, Nevada in 1950 to be married. Her travel within California also has been very limited.

Her father, now dead, was of Austrian descent. He sometimes worked with cattle and he had raised as many as 500 sheep at a time. He had also worked occasionally as a commercial sheep shearer. His children, three boys and four girls, often helped him with the livestock at home and accompanied him while he sheared sheep in the Porterville area.

Attempts to obtain blood specimens from the patient and her siblings were unsuccessful in 1970. Inasmuch as other members of her family apparently had had opportunities for exposure to echinococcosis, we continued our follow-up efforts. In May and June 1971 we were successful in locating the patient's sisters and brothers and in obtaining blood from all of them.* A telephone conversation with the patient convinced us that she apparently was experiencing no difficulties from the continued presence of a possible hydatid cyst.

The results of serologic tests performed at the CDC showed that there was only one positive serum in this group, that of the patient herself. It is presumed that she still has a hydatid cyst and she was advised to obtain periodic medical examinations.

Case 4.

An epidemiologically more significant follow-up occurred in the previously reported case[8] of a 49-year-old Kern County sheep rancher of Basque extraction who died following operation for removal of a hydatid cyst. We found ten of the eleven dogs examined on his ranch to be infected with E. granulosus. Infection in sheep was also found at autopsy, and the patient's brother, also a sheep rancher, had a positive Casoni reaction (5 cm square in area). The indirect hemagglutination test on the brother's blood, performed at the University of California, Davis, gave a diagnostic titer of 1:6400. His chest was normal on radiographic examination and, to date, he has not agreed to a liver scan. The members of the patient's immediate family have also refused so far to submit to serological testing or medical examination. Further attempts will be made.

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*We are grateful to Dr. William DeFries, Fresno, for his willingness to cooperate in this study.

*For their kind cooperation we should like to extend our thanks to Dr. Owen A. Kerns, Bakersfield; Dr. R. F. McBrattney, Visalia; and Dr. I. D. Litwack, Long Beach.

The family's veterinarian was consulted during this investigation and he was advised as to appropriate therapy and prophylaxis for the infected dogs.

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TUBE CECOSTOMY IN PATIENTS WITH COLONIC CANCER

This is known as the bee in my bonnet; but I do pass it on to the younger surgeons. We know that tension inside an anastomosis is dangerous. Tension inside the colon is dangerous. I was brought up never to do a cecostomy. I am sure that many of my colleagues here who are my age or perhaps a little younger heard their chief say the same thing. But I do put this into your minds. If I were having a left colectomy myself, including an anterior resection, I would have a tube cecostomy. We started doing this some 10 years ago. There are five completely different types of surgeons at St. Mark's [hospital in London]—five personality types. I would tell you that all of them are now doing cecostomies.

What we do is use a No. 30 Foley catheter. We put it into the cecum through a pursestring suture. The trick is to put it half way up the ascending colon. Only put 5 cc of normal saline solution into the bag. We have never had to close one. We have had no morbidity except a hemorrhage from a vessel in the abdominal wall. . . . That cecostomy tube is out within seven days. It is essential obviously that if you have a tube in the cecum, unless that tube is patent the whole time, the cecum and the colon are not being decompressed. So a nurse has to inject 100 cc of normal saline solution down the tube every six hours, day and night, to keep it patent. Obviously the cecostomy tube is dangling over the side of the bed; there is no clamp on it.

—Sir Clifford Naunton Morgan, London

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"Pure Pan-Dysautonomia" A Newly Discovered Syndrome

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A FUNCTIONAL AND ANATOMIC SEPARATION of the voluntary and autonomic nervous systems has always been artificial and, in the light of present day knowledge, is no longer tenable. In the laboratory, for experimental purposes, this artificial division has been useful and has led to tremendous advances in physiology, pharmacology and anatomy. In a clinical setting, however, the so-called autonomic part of the patient has been ignored. It is clear, for example, that while respiration is involuntary, or autonomic, it can voluntarily be inhibited. Similarly, sphincter function is classed as autonomic but in a civilized setting, at least, is mostly under voluntary control. Bodily functions which were hitherto considered completely beyond voluntary control are now being increasingly influenced with biofeedback techniques, and voluntary increases in blood flow in rat ears and human hands have been demonstrated.

The recent intrusion of autonomic function into clinical consciousness can largely be attributed to the interest aroused by a number of disorders which are accompanied by spectacular symptoms and signs of autonomic dysfunction. This emphasizes the generally forgotten fact that all normal bodily activities depend, to a large extent, on normal innervation. Dysfunction of the autonomic nervous system intrudes into the practice of cardiologists, nephrologists, ophthalmologists and others, but it remains the province of the discerning neurologist. Clinical assessment of autonomic function is possible. The site of lesions responsible for dysfunctions can usually be recognized and some disorders can be treated.

Primary autonomic neuropathy of auto-immune type,* or "pan-dysautonomia," was recognized clinically in 1969 by Young and coworkers.[1] More recently, a report by Tomashefsky[2] confirmed the existence of this clinical syndrome which appears to be similar to an experimental disease produced in rabbits by the injection of human sympathetic tissue mixed with Freund's adjuvant.[3] In the experimental disorder, an abnormality of reflex vasomotor function related to temperature regulation was found. The disorder was transient and was associated with circulating antibodies to a sympathetic tissue antigen. Unfortunately, similar reflex vasomotor studies, though possible in man, were not carried out in the three patients thus far reported to have had this disease. Pathologic examination of animals with experimental autonomic neuropathy showed mild perivascular lymphocytic infiltrates in sympathetic ganglia in only half the affected animals but on the evidence available, it was concluded that the disorder was due to dysfunction of efferent sympathetic fibers.[3] Clinical accompaniments of the disease in the form of paralysis were rare. This was attributed to a mild superimposed experimental allergic neuritis, probably related to the small amount of myelin present in the antigen used for immunization. Examination of the nervous system in patients with "pan-dysautonomia" has been restricted to the sural nerve in one case, and no abnormalities were found. Whether or not the pathologic features of the disease in man are similar to those found in experimental autonomic neuropathy is not known. The clinical similarity

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*The case of the third patient of record to have this disorder was reported in detail in the Specialty Conference, "Dysautonomia—Its Significance in Neurologic Disease," by Jost Wichser, M.D., Nazhiyath Vijayan, M.D., and Pierre M. Dreyfus, M.D., which appeared in the October, 1972, issue of CALIFORNIA MEDICINE.

of the two disorders suggests that the pathogenesis of "pan-dysautonomia" might be closely related, if not identical, to that of experimental autonomic neuropathy. The situation might be similar to the Landry-Guillain-Barré syndrome and experimental allergic neuritis which, pathologically, mimics the former very closely.[4]

The clinical manifestations of so-called "pure pan-dysautonomia," though initially entirely autonomic, may eventually involve other parts of the peripheral nerves, emphasizing the essential unity of the nervous system. An as yet unpublished case of chronic "pan-dysautonomia," starting at age six, with large, unreactive pupils, decreased salivation and tearing, anhydrosis, hydroureters, atonic bladder and severe postural hypotension, remained unchanged until about age 18, when hypoactivity of upper limb reflexes appeared. The cerebrospinal fluid was normal throughout, but a sural nerve biopsy, done at age 20, showed mild degenerative changes of myelinated fibers and abnormalities in the fiber size spectrum of both myelinated and unmyelinated fibers. In this case, incidentally, reflex vasomotor function was found to be defective just as in experimental autonomic neuropathy.[5]

In the light of more recent knowledge, the classic view of functional antagonism between cholinergic and adrenergic systems is no longer tenable and, at least centrally, reflex autonomic pathways are characterized by alternating adrenergic and cholinergic neurones. It seems also likely that adrenergic brain stem neurones synapse, at least partly, on cholinergic neurones found in the intermedio-lateral cell columns. Moreover, in the periphery, the previously rigidly maintained distinction between cholinergic and adrenergic neurones seems now tenuous. Some cells in sympathetic ganglia are cholinergic, like those controlling sweating, and some vasodilator neurones to blood vessels in muscle. Furthermore, norepinephrine, apart from acting as a neurotransmitter peripherally, may modulate the effect of acetylcholine also. It seems, then, that rigid classification of clinical deficits into sympathetic or parasympathetic is no longer accurate and autonomic disturbances may best be classified on clinical grounds into those related to pupillary, thermoregulatory, vasomotor, sudomotor, visceral (predominantly bladder and bowel), copulatory and sexual dysfunction. One major difficulty in the past has been in the examination of autonomic function, this being an area between internal medicine and neurology where few felt at home and interest was generally lacking. In recent years, spurred by case reports such as those of Wichser and others, a great deal of progress has been made in this borderland, and the use of clinical tests in the definition of the site of lesions and also eventual pathological verification of their extent has shed new light on some disorders of "autonomic activity."

Baroreflex Function

Through the use of Valsalva's maneuver, the functional integrity of baroreflex mechanisms is usually assessed. While blocked responses to Valsalva's maneuver and orthostatic hypotension are evidence of disordered circulatory reflexes and often occur together, only one of these abnormalities may be present in some patients with neurological disease.[6] The reason for the dissociation of these vasomotor responses in some patients is not clear, but it may depend on a return of venous tone or a denervation supersensitivity of chronically denervated vessels which develop increased activity in response to stretch or to normal amounts of circulating catecholamines. In general, chronic loss of baroreflex function, whether in response to falls in cardiac output produced by Valsalva's maneuver or orthostasis or sudden rises in blood pressure, while detectable by special techniques, does not ordinarily lead to the expected consequences; that is, there is usually no symptomatic postural hypotension and in those who cannot regulate their blood pressure in response to sudden rises in systolic pressure, there is no progressive increase in blood pressure despite the loss of baroreflex responses.

Thermoregulation

Though temperature control is an important function of the hypothalamus and its peripheral connections, tests of temperature homeostasis are not often performed, even in a setting of dysautonomia. Ordinarily, derangements in temperature homeostasis are common, especially in the elderly, and may lead to accidental hypothermia or hyperthermia, both conditions being associated with a high mortality.[7] The common clinical practice of measuring mouth or rectal temperature can be shown to give an inadequate measure of rapid changes in hypothalamic temperature which are closely related to thermoregulatory activity in both animals and man. The temperature of the hypothalamus itself is, therefore, the ideal site for the measurement of central temperature. This can be accomplished, for obvious reasons, only in animal experimentation. For most purposes, central temperature can be satisfactorily recorded from the external auditory meatus[8] and in those with poor thermoregulatory control, the monitoring of central temperature should be carried out by a thermistor probe placed in the external auditory meatus. Since clinical manifestations of hypothermia or hyperthermia are not easily recognized, patients with extensive paralysis preventing shivering or those with hypohydrosis or anhydrosis need continuous temperature measurements.

An important means of temperature control is related to blood flow through tissue, particularly the skin. Radiant heating of the skin with a heat cradle induces reflex vasodilatation in the shielded hand. The increase in hand blood flow occurs within ten seconds of heating and promptly subsides to resting levels after cessation of the stimulus. This reflex is obtainable when the circulation to the heated part is arrested and it can be abolished by sympathectomy of the heated area, even though this procedure does not interfere with normal temperature sensation of the skin.[9] The afferent pathways for this reflex extend above the brain stem, and in patients with cervical cord lesions, this reflex is absent. The efferent path for reflex vasodilatation is sympathetic and the response is abolished by cervical sympathectomy.[10] It is important to realize that there are two factors which normally act on central temperature sensitive structures in the hypothalamus and affect the thermoregulatory system in man, one of which is activited by neural afferents from the skin and the other is dependent on the temperature of the blood. Though their relative importance in temperature regulation is uncertain, it is probable that skin receptor activity is responsible for vasomotor adjustments induced by rapid environmental temperature swings, whereas the effect of blood temperature is to compensate for changes in heat production and to prevent overcompensation by skin reflexes.[11] In spinal cord lesions, for example, the changes in blood temperature would still be effective in inducing adjustments of vasomotor control, but only in areas above the level of the lesion, whereas reflex changes are abolished and rapid alterations in environmental temperature may be poorly tolerated by such patients.

Methods used for measuring blood flow in the skin are also useful for determining the presence of reflex vasoconstriction which can be elicited in hand vessels after a single deep breath. This vasoconstriction can also be induced by passive chest inflation under positive pressure and by sudden chest compression in those with paralysis of respiratory muscles. There is no definite evidence for the location of the receptors for reflex vasoconstriction in the hand after a single deep breath, but it is known that afferents enter the spinal cord in the upper thoracic region. In patients with lesions of the spinal cord above the sympathetic outflow to the hand, reflex inspiratory vasoconstriction is preserved. This, then, is a purely spinal reflex, complete in the thoracic cord. The efferent fibers to hand vessels mediating inspiratory vasoconstriction are sympathetic and the reflex is useful in assessing the functional integrity of efferent vasomotor fibers independently of central structures above the spinal cord.[12]

Sweating

Two types of sweating are generally recognized: thermoregulatory sweating, which occurs over the whole body in response to changes in environmental temperature; and emotional sweating, which is usually confined to palms, anxillae and soles of the feet. It is not entirely clear whether thermoregulatory sweating is the consequence of a rise in blood temperature which activates central structures responsible for thermoregulation, or a peripheral heat-sensitive receptor reflexly activates central structures. Either of these mechanisms alone or in combination may produce sweating. The mechanism by which sweating is initiated in hot environments seems to vary with the thermal adaptation of the individual. In non-adapted subjects, an abrupt rise in ambient temperature causes sweating after a delay which correlates with the rise in rectal and external auditory meatus temperatures, but is not related to the temperature of the skin. In adapted subjects, however, under similar conditions, an immediate onset of sweating is observed which is related to the rise in skin temperature and a further increase in sweat secretion occurs which coincides with the elevation of central body temperature.[13] The posture of an individual also influences the rate of sweating. For example, if a normal subject lies on his back in a hot environment, sweating is about equal over the body. Lying on one's side, however, causes a remarkable increase in sweating on the uppermost side and inhibition of sweat gland activity on the other side. It is also noteworthy that standing after recumbency is associated with a change in sweat secretion which increases in the upper part of the body and is inhibited in the legs. The initiation of these reflexes appears to be by pressure applied to the skin.[14] These postural sweat reflexes might influence the results of experimental studies in man and it is not known whether they are related to the observations of unilateral hyperhydrosis in patients confined to bed with a variety of diseases which may have no relation to sweat gland dysfunction.

Vascular Reaction to Skin Injury

When the skin is injured by physical, chemical or bacterial agencies, the vascular reaction is three-fold: the vessels dilate locally; the skin weals, or blisters, locally; and the surrounding skin shows a bright red flare which is due to a spreading dilatation of small vessels. This reaction has been called the triple response of Lewis. It has been shown that the flare component of the triple response was absent in denervated skin, though the normal triple response could be elicited for a few days after section of a peripheral nerve until it degenerated. Thereafter, only a central red area without the spreading flare was seen. Transsections of dorsal roots have no effect on the flare, whereas dorsal root ganglionectomy abolishes the flare component of the triple response after seven or more days.[15] This provides direct evidence in man that the integrity of afferent fibers which stem from dorsal root ganglion cells is essential for the diffuse cutaneous vasodilatation which forms part of the normal response of the skin to injury. The efferent, somatic or autonomic nerve supply is not involved since this remains apparently undisturbed by dorsal root ganglionectomy. Furthermore, there is a close relationship between the initiation of the flare and the activity of afferent fibers related to pain.[16] Though it has been shown that the flare component of the triple response persists for some time in skin deprived of its connection with the central nervous system until the appropriate cutaneous nerves degenerate, more recent studies have established that in intact individuals the central nervous system influences this response. For example, in transsections of the cord, the flare in anesthetic dermatomes is smaller than in normal dermatomes.[17] In lesions involving the spino-thalamic tract or thalamus, the flare response is smaller in extent on the affected side when compared to the uninvolved side, whereas lesions involving both the deep and superficial supply territories of the middle cerebral artery, presumably interfering with function of the sensory cortex, show evidence of a larger flare component of the triple response on the involved side of the body.[18] It is clear that while the flare component is absent in the Riley-Day syndrome and in cases of familial congenital universal insensitivity to pain with anhydrosis,[19] this seems to be a manifestation of dysfunction of small dorsal root ganglion cells and axons independent of structures which are usually classed anatomically within the autonomic nervous system.

Paradoxical Hypotension-Hypertension

The paradoxical situation is occasionally encountered when symptomatic postural hypotension occurs in association with recumbent hypertension. Occasionally, such patients are referred for the treatment of their hypertension. Though the number of reported cases[20,21,22] is small, a scrutiny of patients with so-called idiopathic orthostatic hypotension may reveal a surprisingly large number whose blood pressure rises to hypertensive levels during recumbency, particularly after prolonged upright tilting. Recent studies have indicated that the post-tilt hypertension is closely related to plasma renin concentration.[23] In normal subjects, plasma renin levels increase while they are upright. Though impairment of this response in idiopathic orthostatic hypotension has been reported,[24,25,26] other investigators have found normal or exaggerated plasma renin concentration in such patients.[27,28,29] An explanation for these divergent findings seems to be provided by a recent study in which patients with orthostatic hypotension due to lesions of the afferent paths of the baroreceptor reflex were found to have pronounced increases of plasma renin concentration with upright posture, whereas those thought to have baroreflex dysfunction due to a block of the efferent sympathetic path failed to show the normal increase in plasma renin concentration when tilted to the upright position.[23] Recumbent hypertension occurring in association with orthostatic hypotension may, therefore, be a feature of patients who have a lesion of the afferent path of the baroreceptor reflex arc.

Effect of Spinal Cord Lesions

Spectacular disturbances of autonomic function or autonomic hyperreflexia occur, of course, in association with lesions of the spinal cord. Recent studies on tetraplegics with chronic localized complete lesions of the cervical cord above the sympathetic outflow have resulted in interesting new information about autonomic reflex function of the isolated cord.[30,31,32] It was found that both spontaneous and induced muscle spasms resulted in an increase in blood pressure and venous pressure. The heart rate decreased, presumably due to the activity of intact arterial baroreceptors. There was also a decrease in hand and calf blood flow, the hand blood flow reflecting mainly flow through skin vessels, whereas blood flow in the calf is predominantly through muscle. These changes occurred within two to three seconds of a spasm and were independent of changes in bladder pressure. The increase in blood pressure was attributed solely to the vasoconstriction in skin and muscle vessels. In the context of the experiments, it was reasonable to infer that this was the result of a spinal sympathetic reflex to somatic afferents associated with muscular contraction. In a companion study, cardiovascular reflex responses to cutaneous and visceral stimuli in the same subjects were examined. Pinprick and cold applied to the skin above the lesion and noise from a gunshot produced no response. All these stimuli would be expected to induce cutaneous vasoconstriction in normal subjects. When pinprick and cold were applied below the lesion, an increase in blood pressure, bradycardia, venous constriction and a decrease in hand blood flow were observed. All these responses must indicate active arterial vasoconstriction and because of the short time between stimulus and response, these changes must have been reflex in nature. The response to the application of cold below the lesion also indicates that some measure of reflex control of temperature may be preserved in tetraplegic man. These phenomena illustrate again the overlap between somatic and autonomic activity, function of either being influenced by stimuli in the other system.

Further experiments on these patients to assess the effects of head-up tilt on blood pressure heart rate, forearm blood flow, and venous pressure in the hand were performed. After tilting, there was typically a fall in blood pressure and rise in heart rate which continued for about two minutes, then reached a plateau. After the return to the horizontal, the heart rate returned to resting levels within one minute, but a slight overshoot in blood pressure was observed over a period of a few minutes. In contrast to the events observed in normal subjects, no immediate overshoot was seen. Muscle blood flow decreased to very low levels and venous constriction occurred during head-up tilting. These responses were present without muscle spasm or changes in bladder pressure. In these patients, extreme degrees of hypotension were observed without loss of consciousness, an observation similar to that made in patients with Parkinson's disease treated with levo-dopa.[33] The decrease in peripheral blood flow during head-up tilting in tetraplegics in the presence of a fall in blood pressure was attributed to active reflex vasoconstriction, the afferent stimulus being probably in the low pressure system of the intrathoracic or abdominal vascular beds. These cardiovascular reflexes appear to be complete in the isolated spinal cord. Whether or not reflex spinal vasoconstriction is important in the maintenance of blood pressure during tilting in normal subjects or whether this is one possible mechanism by which some measure of blood pressure maintenance in the face of orthostasis is eventually achieved in tetraplegics and those with chronic loss of baroreceptor function from other causes has not been established.

Orthostatic Hypotension

Orthostatic hypotension is often found, if looked for, particularly in the elderly. This may be symptomatic, but more often is not. Symptomatic orthostatic hypotension in this age group is often due to misuse of psychoactive drugs. Cessation of their administration will usually result in improvement. Disabling orthostatic hypotension of the idiopathic variety is best managed by the administration of small doses of ergotamine. This drug has a specific constrictor effect on capacitance vessels[34] and even in patients in whom it may be contraindicated because of arterial disease, the small doses used have been found very effective in the control of symptoms related to postural hypotension.

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DIAGNOSING PULMONARY EMBOLISM: LUNG SCAN IN PATIENTS WITH CHEST INFILTRATE?

It's often said that the patient who has an infiltrate in his chest should not get a lung scan because you can't interpret the result or at least you can't interpret the cause of the infiltrate. Do you agree with this statement?

No, I would definitely disagree, the point being that frequently an infiltrate will show up in just part of the lung. It's true the lung scan will be positive in that area, that is, it will show decreased activity, and this in itself does not help to prove or disprove that the lesion is due to embolism. But in these patients, very often we will see other areas that are devascularized and the film in those areas is normal; this gives you almost conclusive evidence that the underlying diagnosis is pulmonary embolism.

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Specialty Conference

Complications of Antibiotic Therapy

Moderator: IRWIN ZIMENT, M.B., M.R.C.P.
Discussants: PETER V. D. BARRETT, M.D., GILDON N. BEALL, M.D., RICHARD J. GLASSOCK, M.D., MATTHEW O. LOCKS, M.D., MICHAEL LUBRAN, M.D., PH.D., JAMES R. NELSON, M.D., RONALD M. REISNER, M.D., KOUICHI R. TANAKA, M.D., AND IRWIN ZIMENT, M.B., M.R.C.P.

This is a transcription of the regular teaching conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance. The transcription was edited by Drs. Jerrold Turner, Irwin Ziment and Lucien B. Guze.

IRWIN ZIMENT, M.B., M.R.C.P.*

FOR THE PURPOSES OF THIS SYMPOSIUM the term *antibiotic* will not be strictly defined, but will embrace the commonly administered antimicrobial drugs—that is, the systemic antibacterial agents, the tuberculostatic agents, the sulfonamides, the "urinary disinfectants," and the major antifungal agents. We will be employing the commonly accepted loose interpretation of the word, and we will avoid committing ourselves to a strict pharmacological definition.

Thousands of naturally-occurring antimicrobial agents have been isolated and studied, but the vast majority are far too toxic for therapeutic use. Fewer than 50 agents have general clinical application, and only the more important will be considered in this symposium.

Antibiotics differ from other powerful pharmacological agents in their limited therapeutic range of application; they rarely have any practical beneficial medical properties apart from their specific antimicrobial activity. The clinical use of antibiotics is always accompanied by the risk of complications, which range from minor discomfort to fatal reactions. Antibiotics probably have a greater propensity to cause hypersensitivity reactions than any other class of drugs.

Although the penicillins are among the safest and most effective antibiotics in usual dosage, they cause more hypersensitivity reactions than any other agent. The widespread use of the penicillins coupled with an estimated 5 to 10 percent incidence of reactions, including 100 to 300 deaths per year in the United States,[1] accounts for considerable overall toxicity. Drugs of the antituberculosis group cause the greatest variety of hypersensitivity reactions, as well as direct toxic effects; paraminosalicylic acid (PAS) is perhaps responsible for the most protean toxic side effects, but it rarely causes anaphylaxis. Most of the other groups of antibiotics have more direct

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toxicity, and the agents with a Gram-negative spectrum are mostly very toxic, causing serious complications if administered in excessive dosage. Although the modes of action of most antimicrobial agents have been elucidated in considerable detail, understanding of the mechanisms of their toxic effects is relatively incomplete.

In this symposium we will cover the major complications of antibiotic therapy with relation to specific organ-systems rather than by considering the drugs individually. A very extensive catalogue of the complications of all the microbial agents is provided in Meyler's book.[1] The topic of allergic reactions to antibiotics from a general point of view is covered by Kasik and Thompson in their recent article.[2] A useful general discussion of drug toxicity is provided by Cluff.[3] The participants in this review will be more selective and discursive and will not attempt to mention every known complication.

The complications of antibiotic therapy can be divided into five categories (Table 1):

1. Irritative reactions related to the method of administration of the drug, such as pain and erythema at the site of intramuscular injection, or phlebitis from intravenous administration.

2. Direct toxic actions of many antibiotics occur mainly as a result of excessive accumulation of an agent. The damage may be extremely severe, particularly in the kidney, the inner ear and nervous system, the bone marrow and the liver.

3. Superinfection primarily affects the mouth, the gastrointestinal tract, the respiratory tract and the skin. Broad-spectrum antibiotics admin-

TABLE 1.—*Complications of Antibiotic Therapy*

Complication	*Mechanisms*	*Susceptible Organs*	*Examples*
1. Local effects	Irritation at site of administration.	Muscle	Polymyxin, cephalothin, penicillin, tetracyclines, erythromycin, streptomycin, chloramphenicol, kanamycin, carbenicillin
		Vein	Amphotericin, cephalothin, erythromycin, tetracyclines, nafcillin, carbenicillin
2. Direct Toxicity	Pharmacologic side-effects, or from accumulation due to excessive dosage or decreased excretion.	Kidney	Kanamycin, polymyxin, vancomycin, viomycin, amphotericin, gentamicin, cephaloridine, neomycin, streptomycin, sulfonamides, tetracyclines, nitrofurantoin, capreomycin
		Ear	Kanamycin, gentamicin, streptomycin, neomycin, vancomycin, viomycin, capreomycin
		Bone Marrow	Chloramphenicol, nitrofurantoin, sulfonamides, methicillin, rifampin
		Liver	Erythromycin (estolate), isoniazid, PAS, ethionamide, pyrazinamide, tetracyclines, rifampin, capreomycin, lincomycin
		Bowel	PAS, pyrazinamide, ethionamide, tetracyclines, lincomycins, ampicillin, erythromycin, chloramphenicol, nitrofurantoin, nystatin, griseofulvin, cephalosporins
		Eye	Ethambutol, chloramphenicol, isoniazid, streptomycin, ethionamide, nalidixic acid
		Skin	Tetracyclines, penicillin, sulfonamides, isoniazid, griseofulvin
		Nervous System (A) central	Penicillin, carbenicillin, cycloserine, cephalothin, cephaloridine, tetracycline, isoniazid, nalidixic acid, polymyxins, streptomycin, kanamycin, sulfonamides, nitrofurantoin, griseofulvin, amphotericin

(Continued next page)

Table 1, continued

		(B) peripheral	Polymyxins, neomycin, kanamycin, isoniazid, nitrofurantoin, streptomycin, sulfonamides, amphotericin, griseofulvin, ethionamide, ethambutol
3. Superinfection	Alteration of normal flora.	Gastro-intestinal tract	Tetracyclines, ampicillin, chloramphenicol, penicillin + streptomycin, oral neomycin, oral kanamycin, oral cephalosporins
		Respiratory tract	All broad-spectrum agents
		Skin	Broad-spectrum topical and systemic agents
4. Hypersensitivity	(A) Antigen-antibody reactions.	Whole body— anaphylaxis serum sickness drug fever	Most agents
		Specific organs— dermatitis nephritis pneumonitis hematologic reactions vasculitis	Most agents can affect several organs
	(B) Immunologic phenomena	Serologic (anti-nuclear factor)	Isoniazid
		Collagen-vascular (systemic lupus erythematosus)	Isoniazid, griseofulvin, sulfonamides, penicillin, tetracyclines, PAS
5. Miscellaneous	(A) Genetic abnormality	Blood (various enzyme deficiencies)	Nitrofurantoin, sulfonamides, nalidixic acid, chloramphenicol, PAS
		Bone marrow	Chloramphenicol, sulfonamides, amphotericin
	(B) Fetus	Ear	(?) Streptomycin
		Teeth	Tetracyclines
		Teratogenic effects	Tetracyclines
	(C) Immaturity (neonates)	Brain (kernicterus)	Sulfonamides
		General (gray syndrome)	Chloramphenicol
		Teeth (staining)	Tetracyclines
	(D) Pregnancy	Liver (hepatic necrosis)	Tetracyclines
	(E) Abnormal laboratory finding, without definite organ damage	Abnormal liver function test	Newer penicillins, cephalosporins, lincomycins, gentamicin, nitrofurantoin, nalidixic acid, isoniazid, cycloserine, rifampin
		Increased prothrombin time	Broad-spectrum antibiotics, sulfonamides, PAS
		Decreased prothrombin time	Griseofulvin, rifampin
		Positive Coombs test	Cephalosporins, penicillins
		Hypokalemia	Amphotericin, para-aminosalicylic acid, viomycin
		Hypocalcemia	Viomycin
		Methemoglobinemia	Sulfonamides
		Increased porphyrin excretion	Griseofulvin, sulfonamides
		Interference with chemical tests	Various (for details see section on Alterations of Laboratory Tests, by Dr. Lubran)

istered to a debilitated host are particularly dangerous in this respect, since they may pave the way for unusual opportunistic organisms.

4. Hypersensitivity reactions of various types are some of the most common complications of antibiotic administration. These reactions may involve the body generally, or may affect a single organ. Drug fever is a fairly common side effect, and may occur in the absence of other clinical signs of hypersensitivity. Various patterns of fever may occur, but resolve within a few days of discontinuing the drug. Immunologic disturbances are being recognized with increasing frequency. Thus the development of systemic lupus erythematosus has been attributed to the administration of at least seven antibacterial agents.

5. Certain drug reactions are related to the particular susceptibility of the individual. Unusual reactions may occur as a result of genetic defects leading to enzyme deficiencies, such as glucose-6-phosphate dehydrogenase deficiency. Neonates are susceptible to special side effects of tetracyclines, chloramphenicol and sulfonamides. In pregnancy, women are liable to severe hepatic damage if given tetracyclines, whereas this rarely occurs in the non-pregnant.

Any classification is convenient as a summary, but it will be inadequate in that it fails to provide for the full range of antimicrobial drug side effects, and it will imply a greater understanding of the mechanisms than is at present available. Dr. Beall will enlarge on this theme in the following section where the nature of the allergic reaction will be detailed.

Complications of Antibiotic Therapy—An Overview

GILDON N. BEALL, M.D.*

THE MECHANISMS underlying the occurrence of most adverse drug reactions are not well understood. Many are thought to be allergic, either because some immunological changes have been found or because the drug-induced disease is clinically similar to an allergic disease of man or animals. Such clinical criteria for classification of reactions as "allergic" are unreliable. In addition, allergic reactions to drugs may take unanticipated forms. Several of the organ-specific reactions considered in this review demonstrate that unusual patterns of disease do not rule out an immunological cause. These considerations attest the importance of careful immunological investigations in these patients. With rapid advances taking place in immunology, it is almost certain that the fundamental mechanisms involved in many drug reactions will be clarified in the near future.

In this section, I will offer a classification of drug reactions. This will be followed by some discussion of their frequency and the factors that control individual susceptibility. Then, a more specific discussion of adverse drug reactions which mimic disease usually associated with hypersensitivity mechanisms will precede consideration of the diagnosis, prevention and treatment.

Classification of Drug Reactions

A large proportion of drug reactions involves a pharmacological effect of the drug. Such reactions may be further categorized as *overdosage, intolerance,* or *side effects,* depending largely on the aims and point of view of the physician. The overdosage can be due to an error in dosage or an abnormality in the absorption, distribution, catabolism or excretion of the drug. Identifiable genetic defects account for some of these abnormalities, and more will certainly be found. Disease of organs such as the liver or the kidney may predispose the patient to overdosage or intolerance because of failure to detoxify, catabolize or excrete the drug. Side effects are pharmacologic effects of the drug which are unwanted in the situation at hand. The pattern of pharmacological effects of a drug vary from one patient to the next so that ordinarily unimportant side effects represent severe problems in some patients.

Reactions which are unanticipated from knowledge of the pharmacological actions of the drug are called *idiosyncratic* reactions. The cause of most of these reactions is obscure. Some may be due to enzymic defects, such as the idiosyncratic reactions that occur in patients with glucose-6-phosphate dehydrogenase deficiency. Finally, there are *allergic* reactions to drugs. In these instances, immunological phenomena can be discovered, providing evidence that the adverse drug reactions are due to hypersensitivity.

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Hypersensitivity reactions have been conveniently classified by Coombs and Gell.[4] Type I reactions involve skin sensitizing antibodies or reagins (such as IgE), and include asthma, allergic rhinitis and probably anaphylaxis. The reactions are the result of the release of mediators (such as histamine and the slow reacting substance of anaphylaxis). Serum complement is probably not involved in these reactions. Type II reactions (cytotoxic) involve antigens which are part of or are attached to a cell surface. Interaction of these antigens with specific antibodies with or without the participation of serum complement can damage the cell. Penicillin-induced hemolytic anemia is an example of this type of allergic reaction. Type III hypersensitivity involves antigen-antibody complexes. Such complexes may be deposited far from their site of production or entry into the body. Where they are deposited they excite inflammatory processes, often, but not exclusively, with the participation of serum complement. Serum sickness reactions are usually Type III allergic reactions, but some of the serum sickness-like urticarial reactions induced by drugs are probably Type I allergy.

Type IV hypersensitivity involves sensitized cells (small lymphocytes) which react specifically with antigen without the participation of detectable antibody. The reaction releases substances (lymphokines) capable of producing such effects as cytotoxicity, blastogenesis, and inhibition of macrophage migration. Contact dermatitis due to medicinals falls into this category. The recent development of methods for studying delayed hypersensitivity *in vitro* should clarify the role of this mechanism of hypersensitivity in other drug reactions.

Rates of Reactions to Drugs

An epidemiologic study of adverse drug reactions was made by Smith et al.[5] In 900 patients they found an overall incidence of adverse drug reactions of 10.8 percent. The incidence was much greater in patients who received many drugs than in those who received few. For example, of 35 patients who received from 16 to 20 drugs, 40 percent had some adverse drug reactions. The incidence of adverse drug reactions was also increased in patients with abnormal hepatic or renal function. In patients with blood urea nitrogen over 40 mg per 100 ml, 25 percent had adverse drug reactions. Although Smith et al were able to show that the frequency of adverse drug reactions was greater in patients who had given a history of a previous reaction, they did not find an increased rate of adverse drug reactions in patients with an atopic history (for example, asthma or hay fever). With specific reference to Type I allergy, however, Levine has collected evidence indicating that a reaginic response to penicillin is much more frequent in atopic than non-atopic patients. These patients are also the ones who are more likely to have anaphylactic or urticarial reactions to penicillin.[6]

TABLE 2.—*Rates of Reactions to Antibiotics*

Drug	*Main Adverse Effects*	*Rate %*	*Ref.*
Tetracycline	Nausea, vomiting, diarrhea	6.1	7
Streptomycin	Tinnitus, vertigo, rash	12.5	7
Colistimethate	Renal toxicity, neurologic symptoms	25.1	8
Ampicillin	Erythematous rash	9.5	9-11
Other penicillins	Urticaria	4.5	9
Penicillin G	anaphylaxis	0.004-0.015	12

Rates of Reaction to Antibiotics

Table 2 shows some reaction rates (incidence of unwanted effects) for drugs in which this has been studied carefully. Most agents have not been studied sufficiently to make this data available. It is notable that the reaction rates to ampicillin are not as great as with some other drugs although the total number of penicillin-related reactions is large. It has been reported that the incidence of erythematous eruptions with penicillin is 9.5 percent and this incidence climbs almost to 100 percent if the patient has infectious mononucleosis.[9-11] This interesting association is not well understood at present. The incidence of anaphylaxis from penicillin administration has been estimated at 0.004-0.015 percent and it is said that 9 percent of such reactions are fatal.[12]

Antibiotic Reactions Resembling Diseases Known to be Due to Allergy (Table 3)

Anaphylaxis. The antibiotics listed in Table 3 have all been reported to produce anaphylaxis.

TABLE 3.—***Hypersensitivity Diseases Due to Antibiotics***

Anaphylaxis
- amphotericin
- cephalothin
- demethylchlortetracycline
- methicillin
- nitrofurantoin
- para-aminosalicylic acid
- penicillin
- streptomycin
- sulfonamides (several)
- tetracycline

Asthma
- penicillin inhalation

Serum sickness
- penicillin
- cephalothin
- chlortetracycline
- novobiocin
- streptomycin
- sulfonamides

Stevens-Johnson syndrome
- sulfonamides
  - sulfamethoxypyridazine
  - sulfadimethoxine
- penicillin

SLE *(or* SLE*-like) syndrome*
- griseofulvin
- penicillin
- isoniazid
- para-aminosalicylic acid
- sulfonamides
- tetracycline
- streptomycin

Allergic vasculitis
- sulfonamides
- penicillin
- chloramphenicol
- streptomycin

Penicillin is, of course, the most important because of the frequency of its administration. It is suspected that these reactions are Type I hypersensitivity since positive immediate wheal and flare skin tests can be produced with appropriate antigens, and anaphylaxis is more frequent in atopic than nonatopic persons. Asthma seems to be an uncommon complication; it has been described following inhalation of penicillin in sensitive patients. Presumably, this could happen following inhalation of other antibiotics as well.

Serum sickness reactions have been associated with all the different penicillins and with many other antibiotics. Animal studies of serum sickness have indicated it is a Type III (complex mediated) disease. IgE, IgG and IgM antibody formation has been described in drug-induced serum sickness but there has not been a clear demonstration of antigen-antibody complex deposition in vessels. Some reports have indicated a depression of serum complement in serum sickness which would support the idea that complexes are involved. It is possible that both Type I and Type III hypersensitivity can produce a drug-induced serum sickness. Further studies are needed to clarify this situation.

The Stevens-Johnson syndrome has been repeatedly ascribed to long-acting sulfonamides although some questions about this association still exist. Stevens-Johnson syndrome has been reported following treatment with other sulfonamides and penicillin as well. Nothing is known about the possible immunological basis of Stevens-Johnson syndrome.

A syndrome resembling *systemic lupus erythematosus* (SLE) has been reported after administration of several drugs, including such antimicrobials as penicillin, isoniazid and griseofulvin. Some insight into the mechanism of this phenomenon is provided with the knowledge that isoniazid can denature DNA and the antinuclear factors produced in patients taking isoniazid bind more specifically to isoniazid-denatured than native DNA. The renal pathology in SLE is characterized by deposits in the glomerular basement membrane, at least some of which are DNA-anti-DNA antigen-antibody complexes (Type III allergy). It is likely that the drug-induced SLE syndromes will be found to have similar mechanisms of pathogenesis when appropriate investigations are performed.

Allergic vasculitis or polyarteritis nodosa has been described in patients receiving penicillin and sulfonamides and attributed to those agents. Chloramphenicol and streptomycin have also been implicated as causes of polyarteritis. The acute vasculitis of experimental serum sickness (a Type III reaction) has been put forward as a possible model of polyarteritis. However, drug-anti-drug complexes have not yet been demonstrated in the human vascular lesions of polyarteritis.

Diagnosis of Adverse Drug Reactions—Immunological Test Procedures

Where reaginic or IgE mediated allergic reactions (Type I reactions) are involved, a skin test using an appropriate antigen will produce a wheal and flare reaction in 15 minutes. Many adverse drug reactions, however, almost certainly do not involve IgE antibodies and skin tests are not helpful. In addition, the choice of an appropriate antigen or hapten is critical. Skin testing for penicillin allergy requires the use of two different kinds of materials, penicillolyl-polylysine and a minor determinant mixture. Neither of these materials is readily available. The penicillolyl hapten is apparently the major antigenic determinant of penicillin G, but a group of haptens apparently including benzylpenicillin itself are also important. Levine's studies indicate that one can predict anaphylactic sensitivity in patients who have positive skin test reactions to both mixtures.[13] It is hoped that these materials will be generally available in the near future.

Skin testing can be hazardous; preliminary scratch testing and adequate dilution of the suspected material are mandatory, particularly if the testing is being done to determine the cause of an anaphylactic reaction. If no personal experience or published information exists about the material for which skin testing is being contemplated, then the procedure should be regarded as a clinical experiment and subjected to the kinds of scrutiny reserved for experimentation.

It would be desirable if the biologic phenomenon of skin testing could somehow be transplanted to a test tube. An approach to this has been made by the use of techniques in which leucocytes from sensitized patients are challenged with antigen *in vitro* and the release of histamine into the supernatant fluid is measured. This system detects reaginic antibodies. There is some evidence that it is useful in penicillin hypersensitivity. Some workers have used mast cells or basophils from animals in similar *in vitro* tests which have been monitored either by histamine release or by observation of degranulation of the amine-containing cells. To date, the results of these procedures have not been sufficiently reliable to make them useful as diagnostic tests. Another technique which has been investigated depends upon the transformation and blastogenic change of leucocytes *in vitro* following exposure to drugs which have produced reactions *in vivo*. Further study of this reaction is definitely needed.

Patch tests are an easy and reasonably reliable way of detecting contact allergens. If the material is a liquid it should be used undiluted. If a solid, it should be dissolved in propylene glycol in order to give a nontoxic concentration. The skin is then cleansed with acetone, and the drug, on a patch, is put on the skin and left for two or three days to see if it produces a miniature reaction of the contact dermatitis type from which the patient is suffering. A similar patch using only the solvent is placed on a nearby area of skin to serve as a control.

Some drugs can be fixed to red cells and the resulting combination used for a hemagglutination test. Such studies usually demonstrate either IgG or IgM type antibodies. These antibodies may have great significance in certain types of hemolytic anemias but their titers may be unrelated to the occurrence of adverse drug reactions in other tissues.

Clot retraction tests are useful in patients suspected of having drug-induced thrombocytopenic purpura. The blood of the thrombocytopenic patient is combined with normal blood (containing a supply of platelets) in two different tubes. A saline solution of the drug is added to one and saline solution only to the other tube. Clot retraction is then examined. Inhibition of clot retraction serves as evidence of an antiplatelet-drug factor in the patient's serum. This test seems to work nicely with quinidine-induced thrombocytopenia. It is not completely reliable in other instances of apparently drug-induced thrombocytopenia, possibly because not all such thrombocytopenic reactions are immunologic in nature.

If no *in vitro* or *in vivo* test procedure is available to verify sensitivity to a drug, it may be desirable, under certain circumstances, to give the patient a test dose. Such test doses are very dangerous. Testing should only be done for a vitally needed drug where there is no substitute, and testing should be postponed until the patient has fully recovered from the initial reaction. The initial dose should be in the microgram range if it is given orally or in the nanogram range if it is given parenterally. It should be recognized that this sort of procedure may cross the vague boundary between medical care and clinical experimentation.

Avoidance of Adverse Drug Reactions

There are some obvious points. Dangerous drugs should be avoided. A careful history, including a history for the specific drug which one plans to use, should be obtained from the patient, and one should believe the patient's statements. One should be aware of drugs to which a genetic predisposition to intolerance occurs and look for evidences of that predisposition. An estimate of renal and hepatic function is desirable. If a reaction develops, the offending agent should be removed. Sometimes manifestations of the reaction can be suppressed with antihistaminics or corticosteroids. Desensitization should be attempted only if there is a life-threatening need for the particular drug in question. The procedures and schedules to follow in performing desensitization are really not as important as the careful follow-up of the patient and observation of reactions as the drug is administered. If the patient has had an anaphylactic reaction in the past, he will probably again have an anaphylactic reaction during the "desensitization." This, however, can be controlled and the effects minimized by the use of antihistamines, epinephrine, steroids, and continued administration of the antigen. In any case, this procedure is very seldom necessary if alternate drugs or forms of treatment are carefully considered.

Renal Complications

Richard J. Glassock, m.d.*

Renal disease, with or without functional impairment, may be complicated by infections, and, of course, diseases of an infectious nature are also frequently accompanied by abnormalities in renal function. Clinicians are frequently confronted with a therapeutic dilemma in the treatment of serious infections with potentially nephrotoxic agents. There are several approaches to this dilemma. First, one may avoid a potentially nephrotoxic agent, even though alternative drugs may be less effective. Second, a potentially nephrotoxic agent may be used with appropriate reduction of dosage. Third, a beneficial agent may be continued in spite of impaired renal function. If the latter course is adopted, the toxic effects at sites other than the kidney must be considered.

No formula can be devised which can answer each individual clinical problem. The choice among these and other approaches depends upon a number of factors, most notably the nature and severity of the infection, the extent of renal disease underlying the infection, the character of non-renal toxicity of the agent employed, and the availability of effective alternative drugs. One extremely important and often very difficult question to answer is whether or not renal abnormalities observed during treatment with potentially nephrotoxic agents are the consequence of the infection or the result of the nephrotoxic drug itself. Examples of situations where this question arises include glomerulonephritis associated with subacute bacterial endocarditis, consumption coagulopathy associated with renal cortical necrosis in the presence of Gram-negative sepsis, and necrotizing papillitis in diabetic subjects with catheter-induced septicemia.

As a general rule, nephrotoxic antibiotics can be used safely and effectively if an appropriate alteration in dosage is observed when renal function is decreased or diminishing.[14] Unless the renal abnormalities observed during therapy can be clearly related to the effects of the agent itself, it is often best to continue the drug if no effective alternative therapy is available.

Table 4 lists some of the antibiotic agents which have been associated with renal complications. The sulfonamides were the first antimicrobial agents in which significant renal problems were encountered.[15] The use of sulfapyridine, sulfathiazole and sulfadiazine in the early 1940's was associated with the finding of crystalluria. The crystallization of sulfonamides in the renal tubule is dependent upon their concentration, and therefore upon the state of hydration of the individual, the urine flow and the urine pH. Extremely acid urine favors the precipitation of most of these agents. High concentrations of the older, less soluble sulfonamides could cause direct toxic tubular injury, and acute renal failure. With the use of modern sulfonamides, hypersensitivity reactions involving the kidney are more common. These reactions include diffuse interstitial nephritis, diffuse glomerulonephritis, and necrotizing arteritis.[15] There does not appear to be any difference among the individual sulfonamides in their propensity to cause this type of abnormality.

The penicillins, including the semisynthetic penicillins, may cause hypersensitivity reactions, particularly of the diffuse interstitial nephritis va-

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TABLE 4.—*Antimicrobial Agents Associated With Renal Complications*

Major Direct Nephrotoxicity	*Minor Direct Nephrotoxicity*
Kanamycin	Gentamicin
Neomycin	Streptomycin
Colistimethate	Sulfonamides
Polymixin B	*Cephalothin
Bacitracin	*Rifampin
Vancomycin	*Capreomycin
Amphotericin	
Cephaloridine	
Viomycin	
Hypersensitivity	*Anti-Anabolic*
Penicillin	*Tetracycline (except doxycycline)
Semisynthetic Penicillins	
Sulfonamides	
Nitrofurantoin	
Para-aminosalicylic acid	

*May cause rise in BUN without other evidence of nephrotoxicity.

riety. The penicillin derivative most frequently incriminated in production of interstitial nephritis is methicillin, and there have been reports of acute renal failure following large doses and prolonged therapy with methicillin.[16] Occasionally, hyperkalemia may develop in patients with oliguric renal failure following treatment with potassium penicillin G in large doses, as this preparation contains 1.6 milliequivalents of potassium per million units.

The cephalosporins have also been associated with reactions of the diffuse interstitial nephritis variety. Cephaloridine has caused acute renal failure when employed in doses of over 6 grams a day.[17]

The aminoglycoside antibiotics, including streptomycin, kanamycin, gentamicin and neomycin, are potentially nephrotoxic agents. The parenteral use of streptomycin, in the early days of anti-tuberculous therapy, was commonly associated with albuminuria, azotemia and diminished glomerular filtration rate in patients receiving more than 4 grams per day.[15] Nephrotoxicity may have been caused partially by the impurities in the early lots of streptomycin. Recent experience has indicated that this agent has probably a very minimal degree of nephrotoxicity when employed in conventional dosage.[15] However, streptomycin may act synergistically with other aminoglycoside antibiotics in inducing nephrotoxicity, particularly when renal function is already impaired. Kanamycin in doses of 25 mg per Kg of body weight or larger, frequently, if not universally, produces urinary abnormalities, with proteinuria, hematuria, casts and the pathologic changes of proximal tubular necrosis. Acute renal failure has been an uncommon event in instances of kanamycin therapy. However, it may occur at high doses and may also be aggravated by concomitant use of other aminoglycoside antibiotics. Kanamycin has been demonstrated to cause decreases in glomerular filtration rate, renal blood flow and maximum urinary osmolality.[18] These abnormalities are entirely reversible and their development is not necessarily an indication to discontinue therapy, particularly if the infection is severe and kanamycin is the preferred agent of treatment. Neomycin, given orally in doses of 4 grams or greater to patients with hepatic and renal disease, may result in the accumulation of significant blood levels which are potentially ototoxic as well as nephrotoxic.[19] This toxicity has occurred in as many as 25 percent of such patients receiving a dose of 8 grams or more a day. Gentamicin has a degree of nephrotoxicity comparable to streptomycin and not as severe as that of kanamycin or neomycin.[20]

The polypeptide antibiotics, polymyxin B and polymyxin E (colistimethate), are nephrotoxic, particularly at higher dosage. Polymyxin B may induce tubular alterations and decrease creatinine or inulin clearance. Again, this effect is potentiated by other nephrotoxic agents. Minimal urinary abnormalities are not necessarily a contraindication to continued therapy. Adverse renal reactions, including acute renal failure, occur in about 20 percent of patients.[8] Most of the reactions are readily reversible upon discontinuance of the agent. Renal complications usually occur in the first three or four days of therapy. A dosage calculated on a weight basis may result in overdosage for patients with above average weight. Dosage based on square root of weight appears to be better.[8] A seldom used antibiotic, vancomycin, has been associated with nephrotoxicity. This was particularly true with the early preparations. Many centers use this agent as their treatment of choice for staphylococcal septicemia in patients on hemodialysis programs, a situation where one need not fear the nephrotoxicity but only the neurotoxicity.

Tetracyclines given in therapeutic dosage interfere with protein anabolism in man as well as within the bacterial cell. The use of these agents in azotemic patients may result in a dramatic worsening in azotemia and clinical condition.[21]

Since most of the agents, with the exception of chlortetracycline, have a prolonged half-life in the serum of uremic patients they should not be used when patients are significantly azotemic.[14] It has recently been shown that the long-acting tetracycline, doxycycline, can be given safely in the presence of azotemia; this is the only tetracycline now recommended for treatment of susceptible infections in patients with renal impairment.

Outdated tetracycline which has been exposed to a warm, moist temperature at a low pH may develop high concentrations of the breakdown products anhydrotetracycline and epianhydrotetracycline. The Fanconi syndrome, sometimes accompanied by azotemia, has been reported with the use of tetracycline preparations containing these breakdown products.[22] Since citric acid has been omitted from most of the formulations of tetracycline, this phenomenon is a disappearing entity in clinical medicine.

A major hazard of therapy with amphotericin B is the development of nephrotoxicity, manifested by the formation of casts, decreased concentrating ability, defective acid excretion, diminished glomerular filtration rates and hypokalemia. In rare instances, continued use of amphotericin B in the face of progressive azotemia has caused chronic irreversible interstitial nephritis.[23] Although amphotericin B therapy may be associated with a depression of glomerular filtration rate by as much as 80 percent, normal renal function will usually be regained upon discontinuance of therapy. Full recovery is less likely when the total course of amphotericin therapy exceeds 5 grams.

Nitrofurantoin has been associated with interstitial nephritis which appears to be reversible on discontinuance of therapy, and paraminosalicylic acid has also, on occasion, been associated with hypersensitivity reactions.

Obviously, those agents which depend upon glomerular filtration rate for their excretion will be retained in the blood of patients with reduced renal function and therefore the dosage must be diminished to avoid potentially toxic serum levels. Recommendations for the use of antibiotics in renal insufficiency have been reviewed recently.[14,24] In general, antimicrobial agents can be divided into three groups with respect to dosage modifications for patients with abnormal renal function. The penicillins, cephalothin, erythromycin, lincomycins and chloramphenicol require little or no reduction in dosage. Since some agents in this group have prolonged half-life in renal failure, high dosage should be avoided. The aminoglycoside and the polypeptide antibiotics, kanamycin, neomycin, gentamicin, streptomycin, vancomycin, polymyxin and colistimethate, are largely excreted by the kidney and require major modifications in their dosage in renal insufficiency. A useful formula for kanamycin therapy is based on precise correlations of antibiotic half-life and serum creatinine levels. A loading dose of 7 mg per kg of body weight followed by a repeat of the same dose every third half-life will achieve therapeutic blood levels without risk of serious toxicity.[25] The kanamycin half-life in hours can be calculated by multiplying the serum creatinine by 3. Thus, a patient with serum creatinine of 10 mg per 100 ml would receive a dose of 7 mg per kg of body weight every 90 hours to maintain therapeutic blood levels. Similar relationships for gentamicin, polymyxin B and colistimethate may be obtained by studying the half-life of these agents in uremic subjects.

Finally, certain antibiotics should not be used if renal impairment is moderate or severe. These agents have significant toxicity and alternate drugs of equal efficacy are available. Included in this group are tetracyclines (with the exception of doxycycline) for the reasons cited, nitrofurantoin because it does not achieve effective tissue levels and it is effective as a urinary antiseptic only when renal function is relatively normal, and cephaloridine because of its decided potential for nephrotoxicity.

Gastrointestinal Complications

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ALTHOUGH THE gastrointestinal tract bears much of the brunt of the complications of antibiotic treatment, most reactions are not of a serious nature.[26] Stomatitis and glossitis occur with a high frequency, especially with the use of broad-spectrum antibiotics, and one often finds that superinfection with Candida albicans is responsible. Candida esophagitis it not an uncommon problem, and this may be a more elusive diagnostic problem than oral Candidiasis. Cessation of antibiotic treatment is often all that is required in a mild infection, but treatment with oral nystatin is very effective in the management of an established infection.

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There are very few antibiotics and antibacterial agents which cannot be included in the list of those that may, on occasion, produce anorexia, nausea, or vomiting. These symptoms are not only distressing to the patient, but in addition they may produce diagnostic confusion for the physician who, for example, may be treating a patient with pyelonephritis and vomiting. Some of the more notorious offenders include the tetracyclines, nitrofurantoin, erythromycin and the anti-tuberculosis drugs such as para-aminosalicylic acid, pyrazinamide and ethionamide. In some series the latter drug is blamed for upper gastrointestinal symptoms of a significant nature in as much as a third of the patients. In most instances it is possible to administer these drugs successfully by advancing the doses in a step-wise fashion and by directing that they be taken with meals. Antacids are sometimes used concomitantly with an antibiotic to quiet a complaining stomach, but it should be kept in mind that aluminum-containing antacids bind tetracycline drugs, thus preventing both the symptoms and the therapeutic effectiveness of the drug. These gastric symptoms are often attributed to "gastritis," but not very much is known about the mechanisms involved. Because of the high frequency of occurrence and the early onset with therapy, changes in the bacterial flora and hypersensitivity are not satisfactory explanations. A direct toxic effect of the drugs is likely, but its precise nature is unknown. On rare occasions, nausea, vomiting and epigastric distress accompanying the administration of a sulfonamide may actually be the result of pancreatitis.[27]

Diarrhea is another frequent complication of antibiotic treatment, presumably due to the proliferation of antibiotic-resistant bacteria and fungi. As an example of this, the frequency of isolation of Candida from rectal swabs was studied in a control group and in patients after at least four days of chlortetracycline. Whereas approximately 6 percent of the control group was found to have Candida in the rectal swabs, after four days of broad-spectrum therapy the incidence was approximately 70 percent. A similar study was also performed after penicillin administration: here the incidence after four days was only 14 percent.[28] It is clear that Candida itself may be a cause of an enteritis, but this is uncommon. The majority of the cases in which diarrhea occurs with antibiotics are probably associated with a shift in the bacterial flora, but again its mechanism is not well understood. Occasionally, severe diarrhea occurs in association with an overgrowth of resistant species of Proteus and Pseudomonas in the bowel; similarly, resistant Staphylococcus aureus strains may become predominant and produce a serious problem. Lincomycin is of particular interest since it has caused diarrhea in 5 to 50 percent of patients; this at times may be very severe, and can persist for several weeks after discontinuance of the antibiotic. Clindamycin appears to be less toxic in this respect.

In post-surgical patients the problem of staphylococcal entercolitis is not rare, although in my experience it seems less frequent now than in the past. In early series a mortality rate as high as 50 percent in patients with staphylococcal entercolitis was reported. The broad-spectrum antibiotics such as the tetracyclines are the most frequently associated predisposing factors, but combination therapy of any type that is used in so-called "gut sterilization" can produce the problem, and even penicillin alone has been associated with this entity. The lesion itself is a superficial necrosis of large areas of the intestinal mucosa, probably produced by a staphylococcal exotoxin. The patients usually manifest this illness with a diffuse watery diarrhea, but in about 10 percent bloody stools, shock and abdominal pain are prominent features.[29] The diagnosis must be made promptly on the basis of the clinical picture and a gram-stain of the stool, and therapy instituted immediately. The gram-stain of the stool usually will show sheets of staphylococci. The use of methicillin or vancomycin by mouth is quite effective and has greatly reduced the mortality rate of this disease.

Another interesting complication of antibiotic therapy related to the intestine is malabsorption brought about by neomycin, kanamycin or para-aminosalicylic acid. Most of the work has been directed toward elucidating the mechanisms associated with neomycin malabsorption, and several factors have been implicated. Alterations in bacterial flora constitute a major factor, but the mechanism by which the change in flora induces malabsorption is uncertain. Changes have been noted in the small intestinal mucosa which resemble those of non-tropical sprue, but are much less severe, and are readily reversible with cessation of treatment. A defect in the hydrolysis of fats has also been demonstrated, apparently due to inhibition of pancreatic lipase.[30] Although this complication of antibiotic therapy is an intriguing one, it really does not represent a common clinical problem.

Hepatic Complications

Many types of drugs, including antibiotics, may produce hepatic dysfunction. These reactions are generally thought to be a result of sensitization, although it is recognized that certain features are difficult to explain on the basis of classic anaphylactic or delayed hypersensitivity. The various types of hepatic dysfunction which result from drugs have been classified into the hepatocellular, hepatocanalicular and canalicular varieties.[31] With the hepatocellular variety, liver function tests performed on the serum mimic those seen in viral hepatitis with transaminase values in excess of 300 units, and commonly over 1000 units. The alkaline phosphatase in these cases is usually less than 15 Bodansky units, a level which is usually associated with non-surgical types of liver disease. The histologic findings are those of diffuse hepatocellular necrosis and inflammation, features that cannot be distinguished from those seen in viral hepatitis. The mortality rate is significantly higher in this group than in the remaining groups, and it varies with the particular agent involved. Among the antibiotics that may be placed in this group are isoniazid, pyrazinamide, ethionamide, and tetracycline. Some of the sulfonamides may also produce this picture.

One of the most thoroughly studied drugs which may cause the hepatocanalicular variety of hepatic dysfunction is chlorpromazine. The mortality rate from hepatic dysfunction resulting from drugs in this category is much lower than in the hepatitis-like group, and biochemical changes mimic those found in obstructive jaundice. Histologically, one expects to find bile stasis and inflammation of the portal triads without a great deal of hepatocyte necrosis. In most instances it is not possible by liver biopsy to distinguish between this type of drug-induced jaundice and extra-hepatic obstruction. Antibiotics which may produce this type of reaction would include the estolate ester of erythromycin, as well as some of the sulfonamides.

The last category, the canalicular variety of hepatic dysfunction, is produced by methyl testosterone and the anabolic steroids. Liver function tests performed on the serum reveal only mild abnormalities of the transaminase and alkaline phosphatase values, and liver biopsy reveals only cholestasis.

Two of the antibiotics mentioned above deserve further comment. In contrast to many of the other antibiotics where sensitization appears to be the major factor, a dose relationship also has been demonstrated with tetracycline. The administration of large doses of tetracycline to women in the third trimester of pregnancy, particularly those with pyelonephritis, or to patients with renal insufficiency can cause hepatic failure. The histopathologic features of this drug reaction are very characteristic, with fine fat droplet deposition in the liver cells. In contrast to the situation a decade ago, a great variety of potent antibiotics is now available, and because of the complications which can occur with high dose levels of tetracycline, there is no longer any indication for treating patients with more than two grams of this antibiotic a day. Erythromycin estolate may produce abnormal transaminase values in 10 to 25 percent of patients treated with this drug, and in an additional 4 percent a condition resembling obstructive jaundice may develop. However, the effect appears to be specific for this ester, and hepatic complications associated with the erythromycin base have not been reported.[32]

Pulmonary Complications

Matthew O. Locks, m.d.*

The lungs are particularly susceptible to superinfection following the administration of antibiotics, although the presence of abnormal bacteria in the sputum must be critically evaluated to distinguish simple colonization from infection. The lungs are relatively immune to the direct toxic effects of excessive accumulations of antimicrobial agents, but 12 antimicrobial agents have been clearly implicated as inducing some form of lung disease.[33] The pathogenic mechanisms responsible for antimicrobial-induced lung reactions originally had been considered as one or more forms of hypersensitivity reactions. However, hypersensitivity alone cannot fully account for the spectrum of drug-induced lung diseases. It is possible that the idiosyncratic reaction, as well as one or more of the allergic reactions, is operative in some, if not all, of the clinical syndromes of antimicrobial-induced lung diseases.

These clinical syndromes include, in rank of increasing frequency of occurrence, systemic lupus erythematosus, polyarteritis, pulmonary eosinophilia, and asthma. In a recent review of patients seen at certain hospitals in New York City, up to 12 percent of the cases of systemic lupus erythematosus were found to be drug-induced.[34] Since patients with systemic lupus erythematosus have a higher propensity for drug reactions, it is possible that in some of them the disease process may have preceded the administration of the drug. However, in others, the systemic manifestations of lupus erythematosus and the presence of antinuclear antibodies were clearly related to the drug. The pulmonary manifestations of the patients with antimicrobial-induced systemic lupus erythematosus appeared in three basic patterns, with some degree of merging of these patterns in individual patients. In one group, the dominant gross pathologic presentation was the involvement of the serous membranes within the thorax. Accordingly, pleuritis, frequently with effusion involving both lungs, and pericarditis with or without significant effusion were the major findings on physical and radiologic examinations. Although the patients were severely ill and had high fever, withdrawal of the suspected agent and the administration of corticosteroids were accompanied in large part by a rapid recovery.

A second group showed changes primarily within the pulmonary parenchyma, with recurrent bouts of cough, dyspnea and chest pain. Physical examination and radiologic findings were consistent with changes suggesting pneumonia, pulmonary infarction, or pulmonary edema. Despite the presence of severe illness, these patients also showed an excellent response, with recovery after corticosteroid therapy. The third group of patients did not fair so well. The pulmonary involvement included a diffuse interstitial infiltration of both lungs with resultant restrictive dysfunction without obstructive airway disease. This was manifested clinically by dyspnea, hyperventilation, poor respiratory excursions of the chest wall and diaphragm, and hypoxemia. Although symptoms were improved by corticosteroid therapy, restrictive dysfunction of the lungs persisted.

A necrotizing vasculitis of the lung, usually as a part of systemic vasculitis, has been associated with the administration of antimicrobial agents.[35] There are sufficient clinical and experimental examples of exacerbations and remissions of the process related to administration and withdrawal of the drug to strongly suggest a causal relationship. The respiratory manifestations of vasculitis frequently include destructive lesions in the upper respiratory tract before the finding of pulmonary lesions. Subsequent changes in the lower respiratory tract resemble pneumonia, pulmonary infarction, pulmonary abscess, and nodular densities of varying size. The constellation of findings included in the description of Wegener's granuloma, with lesions in the upper and lower respiratory tract, as well as the kidneys, is frequently associated with a history of antimicrobial hypersensitivity and the repeated administration of various antimicrobial agents.

Of increasing interest in recent years has been the pulmonary disorder described as pulmonary eosinophilia. Although the clinical syndrome may be causally related to various etiologic agents including parasitic infection, it has also been clearly demonstrated to be drug-induced. Characteristically, the illness is abrupt in onset, with shaking chills, high fever, dyspnea and a cough productive of mucoid sputum. The patient is visibly in respiratory distress with tachypnea, and rales are generally heard in both lungs, but wheezing is notably absent. Occasionally there is a cutaneous eruption. Peripheral eosinophilia is present to variable degree. Chest x-ray films generally show scattered broncho-pneumonic infiltrations with an occasional pleural effusion. Generally, rapid recovery is achieved when the offending drug is discontinued. Infrequently, the illness can persist for several weeks, but fortunately it is responsive to corticosteroid therapy. The most common drug causing pulmonary eosinophilia at present is probably nitrofurantoin.[36] Penicillin, sulfonamides and para-aminosalicylic acid have also been implicated.[37-39]

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Perhaps the most common drug-induced disorder is asthma. This can present as an immediate hypersensitivity reaction purely in an isolated form or as part of a generalized anaphylactic response. Delayed types of asthmatic reactions to antibiotics have also been seen, occurring after repeated administration of the drug. Penicillin, tetracycline, erythromycin, neomycin, streptomycin, griseofulvin, cephaloridine and ethionamide have been associated with one or both types of asthmatic reactions.[40]

Drug-induced disorders of the respiratory tract can occur in circumstances that challenge one's diagnostic acumen. This is especially true when the route of administration of the offending agent may be deceptive. For example, a woman had recurrent episodes of pulmonary eosinophilia which were eventually found to be caused by a vaginal cream containing sulfanilamide.[41]

When evaluating a patient with a respiratory disorder who is receiving or has received a drug, either for treatment or for a diagnostic study, one's index of suspicion should be sufficiently aroused to answer the question "Could a drug (or drugs) be the causative agent?" The history of possible exposure to a drug coupled with the finding of non-specific associated findings such as rash, eosinophilia, or thrombocytopenia suggests the likelihood of a drug-induced disorder. Withholding all drug therapy may also yield the correct diagnosis. By the use of specific testing procedures, including (if considered safe) a provocative challenge, the causative agent or agents may be identified.

Neurological Complications

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The neurological complications of antibiotic therapy are many and varied. Some are produced by a mechanism similar to that responsible for the antimicrobial action of these agents—that is, effects on cell wall synthesis or integrity, interference with energy production by inhibiting oxidative enzymes, or interference with pyridoxine to simulate a vitamin deficiency state.[42,43] Still other effects, such as slowed nerve conduction and a myasthenic-like state, may be due to a reversible interference with acetylcholine release, perhaps through a disturbance of calcium metabolism.

Although the ototoxic effects of antibiotics are by far the most important neurological complications, this review will progress in an orderly fashion from cerebral through peripheral nerve effects.

Penicillin Encephalopathy. A remarkable syndrome of central nervous system hyperexcitability may result from excessively high blood levels of penicillin, usually after administration of more than 60,000,000 units in normal subjects, but occasionally after less than 20,000,000 units a day in the presence of renal failure or preexisting cerebral disease.[44]

Penicillin is one of the most irritating substances when applied directly to cerebral cortex and often is the drug of choice for producing restricted experimental seizure foci. Injection of less than 2000 units into the cortex of monkeys may produce listlessness and intense myoclonic seizures within 3 minutes.[45] Study of single crayfish stretch receptors showed that penicillin decidedly reduced membrane potential differences and thus increased excitability.[46] This effect was dose-dependent and similar to that of ouabain or lithium and possibly resulted from sodium pump deactivation.

Clinically, penicillin encephalopathy is char-

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TABLE 5.—*Action of Ototoxic Drugs on Hearing and Equilibrium*

Drug	*Effect on*		
	Vestibule	*Cochlea*	*Kidney*
Streptomycin	+++	+	+
Dihydrostreptomycin	+	++++	+
Neomycin	+	++++	+++
Kanamycin	+	+++	+++
Vancomycin		+++	+
Viomycin	+++	++	++
Framycetin		++++	
Gentamicin	++		++
Colistin	++	+	++

Meuwissen and Robinson[50]

acterized by delirium or coma with intense myoclonic and generalized seizures. Forty million to eighty million units given intravenously to 17 patients induced seizures in only one patient.[47] However, numerous cases of encephalopathy with less than 20,000,000 units have been reported in the presence of renal failure. In one case a close correlation was demonstrated between the neurological symptoms and the cerebrospinal fluid levels of penicillin.[48]

In the presence of renal failure it has been recommended that 10,000,000 units be given once and then blood levels determined as a gauge for subsequent doses.[14,50] Because passage of penicillin from the blood into the cerebrospinal fluids is slow, single intravenous doses probably are less neurotoxic than continuous infusions.

Of the other antibiotics, cycloserine in doses of greater than one gram a day is particularly likely to cause myoclonic jerking and other seizures.[42,43] These effects are rapidly reversible. Convulsions are also reported after amphotericin B.[42] Cycloserine may also produce dyskinesias, paresis, tremors and dysarthria, which possibly may be due to interference with pyridoxine metabolism. Transient speech disturbances and other untoward neurological reactions have also been reported with polymyxin B and colistimethate.

Aside from the above acute effects, a potential impairment of memory in humans should be anticipated with development of future antibiotics such as puromycin. This agent is a powerful inhibitor of protein synthesis. Evidence to date indicates that long-term storage of memory traces ("engrams") is dependent upon RNA synthesis, and recently Flexner has reported impaired memory in mice with bilateral puromycin injections into the hippocampal complex, the structure most concerned with memory in man and several lower animals.[49]

Ototoxicity of Antibiotics. These effects are among the most common and serious side effects of antibiotic usage, with potential for severe deafness and severe vestibular loss. Fortunately, many of these effects can be avoided with careful selection of antibiotic dosage and attention to early symptoms of inner ear dysfunction. This topic has recently been reviewed in great detail, and a list of ototoxic antibiotics is shown in Table 5.[50] Although previous reports have suggested that the site of toxicity may be the end-organ, cochlear nerve or central nuclei, recent evidence suggests that the loss is overwhelmingly concentrated at the hair cell level of the cochlea or vestibular apparatus, with the infrequently observed central lesions being secondary to transynaptic degeneration.[51]

The predilection of the inner ear hair cells for such damage is unexplained although factors related to the peculiar supply of oxygen to the hair cells or the slow removal of antibiotics from the endolymphatic space may be most important. The hair cells of the cochlea show an abundance of mitochondria and oxidative enzymes which degrade glucose.[50] Because of the peculiar anatomical fact that oxygen must be delivered to the hair cells from the stria vascularis through diffusion across the endolymph, perhaps a relatively greater deprivation of oxygen than seen in other tissues may occur when antibiotics contact the hair cells. Streptomycin combines with a surface component of bacterial walls to increase their permeability, leading to cellular swelling and disruption. Such findings in mitochondrial membranes of the cochlea are prevalent early.[52] Inhibition of protein synthesis may also lead to disruption of the cell.

Clinically, the toxicity may appear gradually with minor tinnitus and high tone hearing loss but if these symptoms are neglected, rapid and severe deafness may result. Since streptomycin, kanamycin and neomycin may be cleared from the endolymph very slowly, cellular damage may progress even though administration of the drug has ceased. Simultaneous renal damage may also prolong the toxic effects. Careful evaluation of renal function before administration of these drugs is obviously essential. Fortunately, many of the drugs that produce greater cochlear than vestibular loss have limited usefulness. Dihydrostreptomycin has been removed from use and neomycin has essentially been restricted to only topical or oral use; an inflamed gastrointestinal tract or denuded skin surface may allow excessive absorption and toxicity may follow oral neomycin therapy.[52]

Kanamycin should be restricted to less than 1 to 2 grams a day, and in the presence of renal failure a total course of less than 5 grams has been associated with complete deafness. Vancomycin is used infrequently and has been largely replaced by the newer penicillins. The vestibular symptoms from the aminoglycosides, and particularly streptomycin, may be acute, with severe vertigo and dysequilibrium. An early symptom, before these severe side effects emerge, may be slight postural vertigo with rapid head movements. If administration of the antibiotic is stopped at this time, additional severe loss may be prevented. The usual dose of streptomycin of 1 gram a day may be given for over a month without difficulty but doses of 2 to 3 grams a day will invariably be associated with symptoms within three or four weeks. The ototoxicity of gentamicin is almost exclusively vestibular.[53]

Ocular Toxicity. Fortunately, effects of antibiotics on the visual system are minimal but toxic retinopathy and optic neuritis have both been reported in association with chloramphenicol and streptomycin therapy.[42,43] The cause and effect relationships are not clear, with underlying malnutrition possibly playing a role. Isoniazid and ethambutol have also been implicated in optic neuritis.

Peripheral Neuropathy. This complication may occur with many of the previously discussed antibiotics including dihydrostreptomycin, streptomycin, neomycin, kanamycin, chloramphenicol, polymyxin B, colistimethate, nitrofurantoin, sulfonamides, amphotericin B and griseofulvin.[42] The syndrome is that of typical metabolic polyneuropathy with symmetrical stocking-and-glove impairment of both motor and sensory nerves. Onset usually will be gradual, with early paresthesias. These are particularly common about the mouth with streptomycin, neomycin, kanamycin, polymyxin and colistimethate. These paresthesias may not necessarily indicate development of peripheral neuropathy, although with nitrofurans and griseofulvin peripheral neuropathy usually follows.

Isoniazid also produces peripheral neuropathy. This effect has been more extensively studied than with other agents and a clear-cut relationship to pyridoxine metabolism has been established. It is hypothesized that INH combines with pyridoxine to form a hydrazine compound that replaces pyridoxal phosphate in several enzyme systems of oxidative metabolism, including aminoacid decarboxylase and several transaminases. A cerebral syndrome with acute delirium has also been noted with isoniazid and perhaps the metabolic cause is similar to that for neuropathy.

Myasthenic Syndrome. One of the most interesting and fortunately rapidly reversible complications of antibiotic therapy is a syndrome of severe weakness of the respiratory muscles and limbs resembling myasthenia gravis but with additional features of pupillary unreactivity and visual changes. Almost 90 percent of the 123 reported cases have appeared in the postoperative period where drugs implicated as synergists to neuromuscular blocking agents such as ether, tubocurarine or other agents have been used.[54] The myasthenic syndrome occurs after administration of neomycin, streptomycin, kanamycin, polymyxin, bacitracin, dihydrostreptomycin, colistimethate and gentamicin. There appears to be little relationship to the route of administration, and the syndrome has been reproduced by a single dose of colistimethate in one patient.

Antibiotics are thought to produce a deficient release of readily releasable acetylcholine, thus accounting for the enhanced muscular response to higher frequency stimulation. Also, this syndrome is quickly reversible by calcium administration, which has been shown to enhance the liberation of acetylcholine. The presynaptic origin of the syndrome is further substantiated by the response of the pupils and gastrointestinal tract to calcium administration. Neomycin has been shown to decrease the concentration of ionized calcium, thus possibly accounting for its effect, although this mechanism may not apply to other agents.

In summary, this review has mentioned several types of neurotoxicity associated with antibiotic usage. The neurotoxic effects do not coincide entirely with the results predicted from the effects of antibiotics on bacterial cell membranes, mitochondrial metabolism or protein synthesis. Further study of these matters is in order, with emphasis on ways to prevent toxicity as has been done with the use of pyridoxine in isoniazid toxicity.

Dermatologic Complications

RONALD M. REISNER, M.D.*

THIS PRESENTATION IS concerned with a few specific entities which because of their hazard to the patient or because of their peculiar interest should be recognized and associated with the causative agent. An old, but highly accurate, dermatologic aphorism states that "any drug can cause any cutaneous reaction in any patient at any time," another way of saying that drug reactions should always be considered in the differential diagnosis of skin eruptions. Thus drug reactions, along with syphilis, remain the two "great imitators" in dermatology today.

Black Hairy Tongue. This peculiar reaction pattern has been associated with a number of drugs.[55] Among the antibiotics it has been particularly associated with the penicillins, chloramphenicol and the tetracyclines, whether given systemically or applied topically in the mouth, as with penicillin troches. Other causative factors associated with the development of black hairy tongue have been poor dental hygiene and excessive smoking. In some patients there is no evident cause.

This is essentially a disease of adults. It is usually asymptomatic, although occasionally when the hairy projections are rather long, they may tickle the roof of the palate or induce retching if the patient has a sensitive gag reflex.

The "hairs" are actually tremendously enlarged projections of the filiform papillae of the tongue due to a defect in epithelial desquamation which results in the development of hyperplastic keratin caps. The pigmentation appears to be due predominantly to proliferation of pigment-producing bacteria trapped in the interstices of the enlarged papillae. The keratin itself also lends some of the yellowish or yellow-tan color to the mass, and trapped food particles undergoing degradation may contribute to the pigmentation.

The initial area of involvement is usually the posterior dorsum of the tongue, and extension is usually forward and laterally. The color of the "hair" may vary from yellow to tan to brown or black. Untreated, the condition may last for months or years.

Therapy consists of removing the causative agent or condition if discoverable, followed by mechanical or chemical removal of the hyperplastic keratin caps of the filiform papillae. This may be most readily accomplished by gentle brushing of the tongue with a toothbrush once or twice a day. This is sufficient in most patients to produce pronounced improvement or complete clearing. At times, more vigorous methods have been used to induce desquamation, including the application of 20 percent podophyllin in alcohol, or of 10 percent (or even higher concentrations) trichloracetic acid. These are obviously much more hazardous modes of therapy and must be undertaken with great care.

Toxic Epidermal Necrolysis. Toxic epidermal necrolysis, also known as the scalded skin syndrome or Lyell's disease, is a serious, at times fatal, cutaneous reaction pattern more common in children, but occurring at all ages. It has been associated with bacterial infection of the skin, measles and a variety of drugs.[56] The two antibiotics that have been most notoriously associated with this particular syndrome are penicillin and the various sulfonamides. Among published cases, about one-fourth of the patients died, but this figure is biased by the tendency to report the more severely affected patients.

The typical sequence of events is initial development of mild erythema of the eyelids with or without associated mild conjunctivitis or stomatitis or mild erythema of the genitalia. This may persist for one or two weeks before the more severe acute stage develops, often ushered in by mild malaise and rise in temperature. Tenderness and then erythema develops in the skin of the body folds, the neck, the axillae, the groin and often around the eyelids. Within 24 hours bullae with clear contents develop at the site of erythema. These rupture promptly, creating moist strips of necrotic epidermis that slide off leaving oozing, weeping areas. Nikolsky's sign can be demonstrated in the areas of erythematous skin by firmly sliding the fingertips across the skin surface to produce a shearing force which results in the removal of a sheet of epidermis, leaving an oozing, weeping, open area. The erythema and blistering rapidly spread to cover most of the body's surface except for the hair-bearing areas, which tend to be spared.

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If this severe cutaneous reaction does not prove fatal at the time of its acute phase, it gradually disappears spontaneously over a one or two week period without leaving residual scarring unless there has been sufficient superimposed local infection to produce dermal damage. As was previously noted, the prognosis may be grave, particularly in infants with extensive involvement of the skin surface.

The most important aspect of management is supportive with nursing care, maintenance of nutrition, fluid and electrolyte balance, and isolation to protect against infection. In cases associated with pyoderma, identification of the causative organism and the initiation of suitable antibiotic therapy are also indicated. There is controversy over the value of systemic steroid therapy, but in some patients systemic steroids given early in the course of the disease have had a favorable effect, especially if they are started before the onset of necrotic and bullous changes.

Fixed Drug Eruption. This intriguing and peculiar cutaneous reaction pattern is characterized by the recurrence in a small limited site, often the size of a nickel or a quarter, of eruption with each systemic administration of the offending drug. It commonly presents as a well demarcated area of erythema and edema which may or may not have a bullous component. This eruption recurs at the same site every time the patient takes the drug, and is limited to that site. The lesions gradually heal by crusting and scaling and very commonly leave an area of marked post-inflammatory hyperpigmentation. The two groups of antibiotics most commonly associated with this reaction pattern are the sulfonamides and the tetracyclines.[57]

General Exfoliative Dermatitis. This very serious complication of antibiotic therapy is associated with serious systemic manifestations and at times, particularly in elderly patients, a fatal outcome. The antimicrobials most commonly associated with the development of generalized exfoliative dermatitis are the sulfonamides and para-aminosalicylic acid, and less commonly penicillin and streptomycin. In one large series, drugs accounted for about 10 percent of all patients with generalized exfoliative dermatitis.[58]

Patients with generalized exfoliative dermatitis undergo profound metabolic and physiologic changes which require careful medical and nursing management. These patients have widespread vasodilatation and cannot vasoconstrict, and hence constantly radiate heat. The patient feels cold, shivers, and the core temperature may fall. A sufficient degree of hypothermia may develop, particularly in elderly debilitated patients, to cause death. This tendency toward heat loss is further aggravated by fluid loss through the skin as evaporative heat loss adds to the radiant heat loss from the dilated vacular bed. Conversely, because of plugging of the sweat glands by the exfoliation, these patients cannot increase their heat loss sufficiently to compensate for warm environments and hence fever or even heat prostration may develop in response to elevated environmental temperatures.

It is important to remember that there are many other causes of exfoliative dermatitis including antecedent dermatoses such as atopic dermatitis and psoriasis. In several large series about 10 percent of patients with generalized exfoliative dermatitis proved to have an underlying lymphoma. Because of the associated reactive lymphadenopathy that may occur with generalized exfoliative dermatitis, careful interpretation of lymphadenopathy and of biopsy of lymph nodes is necessary in evaluation of possible lymphoma. Among physical signs, splenomegaly is probably the most useful indicator of underlying lymphoma in the presence of generalized exfoliative dermatitis.

Photosensitive Drug Eruptions. Another fascinating group of eruptions associated with antibiotic use are the photosensitive drug eruptions.[59] Usually the eruption is confined to light-exposed areas, but the patterns may not always be absolutely clear.

The light reaching the surface of the earth contains wave lengths from about 2,800 Angstroms (Å) to about 18,500 Å—that is, the near ultra-violet through the visible and on into the infrared spectrum. Wave lengths of about 2800 to 3200 Å are the so-called sunburn spectrum, with a peak at around 2950 Å. Ordinary window glass will block out almost everything below the 3200 Å range, the common range for causing photosensitivity eruptions, but the action spectrum for some drugs is higher than 3200 Å. Thus some photosensitive drug reactions may be activated through window glass.

Reactions are of two types: phototoxic and photoallergic. Phototoxic eruptions occur in everybody if the right amount of a drug or its metabolite reaches the skin and is exposed to a sufficient quantity of the right wave length of light. Photoallergic reactions occur only in a very small proportion of people. They have an antigen-antibody basis, with light being simply one factor participating in the development of the reaction. Clinically, photoallergic reactions are of all types — urticarial, exanthematous, plaque-like, nodular, eczematous, and others. Phototoxic eruptions, however, are simply exaggerated sunburn eruptions; phototoxic substances lower the threshold for the development of erythema.

Among the antibiotics, demethylchlortetracycline can cause phototoxic reactions in about 10 to 15 percent of patients. This reaction can deliberately be produced in about 80 percent or more of patients by administering an ordinary dose of 600 mg a day coupled with exposure to the noon-day sun in mid-latitudes in the summer. Even then, about 20 percent of patients do not have a reaction; an undefined factor of individual susceptibility plays an important role. The reaction may be avoided by simply avoiding light exposure; but since the action spectrum for demethylchlortetracycline is between 3500 and 4200 Å with a peak at around 4000 Å, patients must avoid even window-transmitted sunlight. In demethylchlortetracycline photosensitivity the interesting phenomenon of photo-onycholysis, manifested by discoloration and separation of the nail-plate from the nail-bed, may also be seen.

Other antibiotics that produce phototoxic reactions, although much less frequently, are other tetracyclines, sulfonamides, penicillin and occasionally isoniazid. Very commonly, the submental area and philtrum area are spared because of the shadowing effects of the chin and the nose.

Treatment consists essentially in the recognition of the reaction as a photosensitive one and the removal of the offending agent and avoidance of sunlight, or in the case of those antibiotics whose action spectrum is above 3200 Å avoidance of either direct or window transmitted light exposure. Symptomatic therapy with compresses or topical steroids is usually effective. In extensive severe reactions, systemic steroid therapy may be indicated. Protective chemical sunscreens may be helpful, but are often ineffective. Protective clothing, while helpful, may often be unacceptable to the patient for regular wear. The intensity of sunlight is greatest in mid-latitudes from about 10 in the morning to about 3 in the afternoon, and exposure under these conditions should be particularly avoided.

Eruptions Due to Ampicillin. Eruptions due to ampicillin deserve special mention because of their very high incidence and some unusual characteristics of their course.[60] It was noted early that the incidence of eruptions associated with ampicillin seemed to be unusually high. Subsequent experience has demonstrated that the incidence of eruptions due to ampicillin is in part a function of dose. Patients receiving 4 to 8 grams a day for typhoid fever and salmonella infections exhibited an incidence of about 20 percent. In large series of patients receiving smaller doses the incidence of eruptions has varied from about 3 percent to 8 percent. The one intriguing exception to this pattern has been the almost 100 percent incidence of ampicillin eruption in patients with infectious mononucleosis receiving ampicillin regardless of dosage.[9-11] These eruptions are usually rather florid, maculopapular, morbilliform eruptions involving most of the cutaneous surface. In contrast, patients with infectious mononucleosis receiving benzylpenicillin or phenoxymethylpenicillin have shown no increased incidence of skin eruptions. The explanation for this peculiar response in infectious mononucleosis is not known.

It now appears clear that eruptions associated with ampicillin may be divided into two broad classes. The first consists of urticarial eruptions which tend to occur within the first week of ampicillin therapy, and persist or become worse with continued therapy. The second consists of macular, papular, morbilliform rashes which tend to occur after the first week, even up to three weeks after the initiation of therapy. These eruptions may have onset after ampicillin therapy has been discontinued. They follow a variable course and may become worse, remain the same, or clear completely during continued ampicillin therapy. It appears likely that the early urticarial reactions to ampicillin are analogous to those from penicillin and are due to the drug itself, whereas the anomalous late erythematous eruptions which account for the excess incidence of ampicillin eruptions over penicillin eruptions are due to impurities contaminating ampicillin during the course of its manufacture. It has been proposed that these impurities may be protein in nature or may result from polymerization of ampicillin into dimers, trimers and polymers of higher molecular weight—a process which proceeds rapidly in aqueous environments, thus requiring prompt use of ampicillin after it has been reconstituted. A recent study using a highly purified ampicillin preparation from which the majority of the protein impurities had been removed, demonstrated a pronounced reduction (about 50 percent) in the incidence of eruptions observed in patients receiving the drug.[60] It seems likely that the highly purified preparation will become standard preparation and we may look forward to a reduced incidence of cutaneous reactions to ampicillin.

Hematologic Complications

Kouichi R. Tanaka, M.D.*

The significant hematologic complications of antimicrobial drugs constitute a diverse group (Table 6). They develop in only a very small proportion of the population exposed to a drug, and occur, in most instances, unpredictably.

TABLE 6.—*Hematologic Complications of Antimicrobial Therapy*

1. Anemia
   a) Aplastic anemia
   b) Hemolytic anemia
   c) Sideroblastic anemia
2. Granulocytopenia
3. Thrombocytopenia
4. Eosinophilia (allergic response)
5. Positive Coombs test
6. Disorders of hemostasis
   a) interaction with coumarins
      (i) increasing prothrombin time
      (ii) decreasing prothrombin time
   b) other (e.g. bleeding)

Aplastic anemia is the most frequently fatal of these reactions, and, next to agranulocytosis, the most commonly reported. Chloramphenicol is clearly the leading drug implicated in cases of aplastic anemia.[61-65] In the American Medical Association Registry on Adverse Reactions, there were 163 reports of aplastic anemia in which chloramphenicol was the only drug administered; the next most frequent antimicrobial agents implicated were three instances each of sulfamethoxypyridazine and sulfisoxazole.[64] Of 138 persons in California whose death was attributed to aplastic anemia between January 1957 and June 1961, 30 (22 percent) had had therapy with chloramphenicol.[66] From a subsequent study in California, the risk of fatal aplastic anemia from chloramphenicol within one year of exposure was estimated to be between one in 24,500 and one in 40,800.[67] The exact incidence of bone marrow aplasia among recipients of chloramphenicol is not known, but is rare.

Chloramphenicol produces two types of toxicity (Table 7). As yet, there is no evidence that reversible bone marrow suppression and aplastic anemia from chloramphenicol are related. Reversible toxicity is a pharmacologic effect of the drug, but the pathogenesis of aplastic anemia remains unknown. However, the occurrence of chloramphenicol-induced bone marrow aplasia in identical twins[68] as well as *in vitro* metabolic studies on bone marrow from patients who had recovered from chloramphenicol-induced aplastic anemia[62] supports the hypothesis that this complication occurs on the basis of a genetically determined biochemical predisposition. At present there is no reliable way to predict in which patients aplastic anemia may develop after chloramphenicol therapy. Therefore, the wise judgment of the physician concerning the need for the drug constitutes the only effective preventive measure.

Depression of bone marrow has been reported with the use of other antimicrobial agents—for example, various penicillins, sulfonamides, streptomycin, nitrofurantoin and amphotericin. Significant marrow damage as a result of these drugs must be extremely rare, and the true toxicity of various antimicrobials is difficult to evaluate.[69]

Hemolytic anemia is being recognized with in-

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TABLE 7.—*Two Types of Chloramphenicol Toxicity*

Reversible Bone Marrow Suppression	*Aplastic Anemia*
Common	Rare (? genetic basis)
Dose-related	Not dose-related
Reversible	Usually fatal
Occurs concurrently with therapy	Late clinical onset
Cellular marrow usually	Aplastic or hypoplastic marrow
Vacuolization of early erythroid cells	
Reticulocytopenia	
Elevation of serum iron	

TABLE 8.—*Antimicrobial Drugs and Hemolytic Anemia*

Mechanism	*Drugs*
1. Enzyme deficiency	
(A) G6PD deficiency	Chloramphenicol (Caucasians only) Sulfisoxazole (large doses) Sulfamethoxypyridazine N-acetylsulfanilamide Nitrofurantoin Nalidixic acid Para-aminosalicylic acid
(B) Glutathione peroxidase deficiency	Sulfisoxazole Nitrofurantoin
2. Hemoglobinopathy	Sulfonamides
(A) Hemoglobin Zurich	
(B) Hemoglobin H	
3. Immune mechanisms	Penicillin Cephalothin (? other cephalosporins) Isoniazid Para-aminosalicylic acid
4. Unknown mechanisms	Streptomycin Amphotericin B

creasing frequency and is of particular interest because certain pathogenetic mechanisms have been elucidated (Table 8). The most frequent cause of drug-induced hemolysis is glucose-6-phosphate dehydrogenase (G6PD) deficiency;[70] its occurrence is particularly high among Negroes and among Caucasians of the Mediterranean area and of the Middle East. G6PD deficiency is an X-linked trait; thus, males are primarily affected clinically. There is wide variability of expression among heterozygous females. Erythrocytes with deficiencies of 6-phosphogluconic dehydrogenase, glutathione reductase, or glutathione synthetase are also susceptible to hemolysis upon exposure to certain drugs, but these deficiencies are rare. Recently acute hemolytic anemia has been reported following the administration of sulfisoxazole and nitrofurantoin in an adult patient with partial glutathione peroxidase deficiency.[71] Subjects with unstable hemoglobins such as hemoglobin Zürich may also develop hemolysis upon exposure to certain compounds, such as sulfisoxazole.

On rare occasions certain antimicrobial agents cause hemolysis on an immune basis (Table 8). Of these, penicillin has been most frequently implicated.[72] All cases of penicillin-induced hemolytic anemia have been associated with administration of high doses of the drug; all of the patients had received 20 million units a day at some time during their treatment with the exception of one patient who had received 10 million units daily for 26 days. A strongly positive reaction to direct antiglobulin test was noted in all patients at the time hemolytic anemia was diagnosed. The penicillin antibody has been characterized to be IgG and reacts specifically with penicillin-treated red cells. The usual manifestations of penicillin allergy are not necessarily present. Evidence of hemolysis may be present for several weeks after cessation of penicillin administration.

Both cephalothin and cephaloridine not infrequently give rise to a positive reaction to direct Coombs test. The primary mechanism of the positive Coombs reaction has been shown to be the result of nonspecific (nonimmune) binding of a cephalothin (or cephaloridine) protein complex to the red blood cell surface; this is not associated with hemolytic anemia. This phenomenon is of clinical significance only in beclouding crossmatching of blood if the minor match is performed. In rare instances, hemolytic anemia may develop in those patients capable of producing a specific IgG anticephalothin antibody.[73]

Cases of hemolysis have also been described as occurring with streptomycin therapy, but the mechanism is unknown. Similarly, the anemia accompanying amphotericin B treatment has not been fully elucidated, but has been attributed to both hemolysis and marrow depression.

The mechanism of granulocytopenia associated with antibiotics is not known. In the case of chloramphenicol, however, granulocytopenia may be a component of the overall picture of aplastic anemia or it may be a dose-related complication which is reversible and of no serious consequence if the drug is stopped. Most antimicrobial agents have been reported to cause granulocytopenia; in particular sulfonamides, cephalosporins, penicillins, nitrofurantoin, lincomycin and rifampicin have been implicated. The mechanism of this reaction is not understood. Many antimicrobial drugs may also be associated with thrombocytopenia, although there is less evidence for this reaction in the cases of cephaloridine, clindamycin, capreomycin, griseofulvin and the nitrofurans. An immune mechanism for this complication has not as yet been clearly demonstrated.

A bleeding disorder characterized by abnormalities of clotting time and prothrombin time has been described during the administration of carbenicillin.[74] Aggregation of platelets by adenosine diphosphate was substantially decreased in these patients. Antimicrobial agents affecting prothrombin time are discussed in the following section by Dr. Lubran.

In summary, the hematologic complications are diverse. The cytopenias develop in only a very small proportion of the population exposed to the drug, and occur for the most part unpredictably. The pathogenetic mechanism is understood in some, such as in the enzyme deficiency or immune hemolytic anemias, but is poorly defined in most instances.

Alterations of Laboratory Tests

Michael Lubran, M.D., Ph.D.*

Antibiotics and chemotherapeutic drugs may occasionally be responsible for altered values of laboratory test results. These effects (drug interferences) may be due to the following mechanisms:

1. Interference in the actual test. Many broad spectrum antibiotics (for example, tetracyclines) are excreted in the urine as fluorescent metabolites, which interfere in some fluorimetric tests such as those for the determination of catecholamines. Nitrofuran derivatives spuriously elevate creatinine levels by reacting with the color reagent; they also give false positive reactions in glucose tests which employ Benedict's reagent (copper-reducing methods), but not with glucose-oxidase methods.

2. Modification of some physiological function, resulting in a change in some factor. Chloramphenicol may cause an elevation of serum iron and an increase in the saturation of the iron-binding capacity, reflecting a decrease in the iron uptake of the erythroid tissue, which is depressed by the drug.

3. A pathological (usually toxic) effect on some cells or organs or their functions. Almost all antibiotics and chemotherapeutic drugs have been reported to have been hepatotoxic in a few patients. Positive liver function tests (transaminase, alkaline phosphatase, BSP clearance) and elevated bilirubin may occur single or in combination. Some antibiotics (for example, kanamycin, colistimethate) are nephrotoxic and cause changes reflected in blood chemistry and urinalysis. Griseofulvin induces microsomal enzymes which destroy coumarin anticoagulants and decrease the prothrombin time.

4. Modification of some metabolic process (for example, enzyme induction or inhibition; protein synthesis; acting as an antimetabolite; altering the rate of utilization of a substrate). Tetracyclines inhibit protein synthesis, thereby increasing urinary nitrogen loss; if renal impairment is significant, azotemia may result. Novobiocin inhibits glucuronyl transferase; hyperbilirubinemia is associated with the use of this drug in infants.

5. By modifying the effect of another drug (for example by potentiation or inhibition). Sulfonamides potentiate the activity of oral anti-diabetic drugs such as tolbutamide, causing a decrease in blood glucose concentration.

6. By affecting the rate of absorption, metabolism or excretion of another drug. Neomycin, given orally, has been shown to damage the mucosa of the small intestine. Malabsorption, particularly of fat, may occur and the d-xylose absorption test may become abnormal.

7. By altering the degree of binding of another drug to protein carriers in the blood. Sulfonamides displace the coumarin anticoagulants from carrier serum protein, thus enhancing their anticoagulant effect; prothrombin time rises.

8. By interfering with the role of the intestinal bacteria. Broad spectrum antibiotics change the

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intestinal flora and suppress microorganisms producing Vitamin K; prothrombin time consequently is increased.

9. By stimulating the production of antibodies. Penicillin, which in high doses acts as a hapten, may stimulate the production of an antibody, thus giving a positive direct anti-gamma Coombs test.

10. Through metabolic changes in sensitive patients. Griseofulvin and some sulfonamides induce hepatic d-ALA synthetase formation, with a resulting increase in the synthesis of pyrrole compounds. An acute attack of porphyria may be precipitated in sensitive patients. Griseofulvin may increase urinary porphyrin excretion in normal persons.

11. In many cases the mechanism of the drug interference is unknown or conjectural.

Artefactually altered results are not always encountered in patients on antibiotics and chemotherapeutic drugs: some patients appear to be more susceptible than others. This difference may be related to genetically-determined abnormalities (such as G6PD deficiency) or hypersensitivity due to previous exposure to the drug, or to previous or concurrent disease (for example, hepatitis). Usually, however, there is not apparent reason for this idiosyncrasy. Many such side-effects are reported, but some are very rare or are poorly documented. Reported drug interferences due to antibiotics, chemotherapeutic and antifungal drugs are listed in Table 9 (only the more important effects are given[75,76,77,78]). Toxic effects on the formed elements of the blood are discussed in the preceding section on Hematologic Complications, and are not included here.

Conclusion

Dr. Ziment:

This review had covered most of the important and a number of the rare complications of antibiotic therapy, and has delved into some of the mechanisms involved. The range is enormous and is ever-increasing.[79,80] The importance of a thorough awareness of the dangers of antibiotic therapy confronts every practicing physician, since these drugs are in constant use by practitioners in every clinical speciality. The overall problem of drug misuse is of considerable economic importance; as Melmon[81] points out (in a conservative estimate), one-seventh of all hospital days is devoted to the care of drug toxicity,

TABLE 9.—*Effect of Antimicrobials on Laboratory Tests*

Key: ↑ = Elevated; ↓ = Depressed; + = False positive; alt. = Altered (either ↑ or ↓); D = Direct organ toxicity or *in vivo* effect; L = Laboratory finding due to *in vitro* interference with tests: f = Frequent; o = Occasional; r = Rare.

Penicillins and Cephalosporins

1. Urinary "glucose": Benedict's test +, dipstick not affected. (L,f)
2. Plasma catecholamines ↑ (especially ampicillin and carbenicillin). (L,f)
3. Urinary 17-ketosteroids ↓ and 17-hydroxysteroids alt. (L,f)
4. Serum K ↑ (high doses of I.V. potassium penicillin). (D,f)
5. Serum Na ↑ (high doses of I.V. disodium carbenicillin). (D,f)
6. Coumarin anticoagulant effect ↑, prothrombin time ↑ (large doses). (D,f)
7. Serum B-12 ↓ (only in microbiological assay). (L,f)
8. Direct Coombs test + (penicillin, methicillin, cephalothin). (L,f)
9. May cause + L.E. test (penicillin). (L,r)
10. May be nephrotoxic: Albumin, casts, red blood cells in the urine; PSP test abnormal, BUN ↑ (cephaloridine, methicillin, oxacillin). (D,o)
11. May be hepatotoxic (especially carbenicillin and oxacillin): BSP ↑, SGOT ↑, SGPT ↑, bilirubin ↑, alkaline phosphatase ↑, singly or jointly. (D,o)
12. Serum Ca ↓ (methicillin). (D,o)
13. Serum K ↓ and metabolic acidosis (high doses of carbenicillin). (D,r)
14. Urinary porphyrins ↑ (high doses of penicillin). (D,r)
15. Bisalbuminemia (high doses of penicillin). (L,r)

Erythromycins and Lincomycins

1. Urinary catecholamines ↑ (erythromycin). (L,f)
2. May be hepatotoxic (erythromycin estolate, lincomycins). (D,o)
3. Urinary 17-ketosteroids ↑. (L,o)

Tetracyclines

1. Urinary "glucose": Benedict's test +, dipstick not affected. (L,f)
2. Urinary catecholamines ↑. (L,f)
3. Urinary urobilinogen ↓. (D,f)
4. Coumarin anticoagulant effect ↑, prothrombin time ↑. (D,f)
5. Prolonged use may cause laboratory evidence of intestinal malabsorption and steatorrhea. (D,f)
6. Serum cholesterol ↑. (D,o)
7. May be hepatotoxic: BSP ↑, SGOT ↑, SGPT ↑, alkaline phosphatase ↑. (D,o)
8. May be nephrotoxic (BUN ↑ is most common effect, other effects include serum uric ↑, phosphate ↑ and acidosis.) (D,o)
9. Urinary estrogens alt. (L,o)
10. Urinary porphyrins ↑. (D,r)
11. May cause + L.E. test. (L,r)

Chloramphenicol

1. Coumarin anticoagulant effect ↑, prothrombin time ↑. (D,f)
2. Urinary "glucose": Benedict's test +. (L,f)
3. Urinary urobilinogen ↓. (D,f)

4. Tolbutamide potentiated: blood glucose ↓. (D,f)
5. Serum iron ↑, unsaturated I.B.C. ↓. (D,o)
6. Serum bilirubin ↑ in mildly jaundiced patients. (D,o)

Aminoglycosides, Viomycin and Gentamicin

1. Urinary "glucose": Benedict's test +. (L,f)
2. Nephrotoxic. (D,f)
3. Serum cholesterol ↓ (oral neomycin). (D,f)
4. May cause laboratory evidence of intestinal malabsorption syndrome (especially oral neomycin). (D,o)
5. Urine Ca ↑, K ↑, Cl ↑ (viomycin, gentamicin). (D,o)
6. Serum Ca ↓, K ↓, Mg ↓, P ↓, alkalosis (viomycin, gentamicin). (D,o)
7. May cause + L.E. test (streptomycin). (L,r)
8. (?) Coumarin anticoagulant effect ↑.

Polymyxins and Vancomycin

1. Nephrotoxic. (D,f)

Sulfonamides

1. Urinary "glucose": Benedict's test +. (L,f)
2. Serum amino acids ↑. (L,f)
3. Plasma catecholamines ↑ (sulfadimidine). (L,f)
4. Urine discolored brown or yellow. (D,f)
5. Coumarin anticoagulant effect ↑, prothrombin time ↑. (D,f)
6. ^{131}I uptake ↓, PBI ↓. (D,f)
7. Urinary urobilinogen ↑. (D,f)
8. May be nephrotoxic, and cause crystalluria. (D,L,f)
9. May be hepatotoxic. (D,o)
10. Oral antidiabetic drugs potentiated, blood glucose ↓. (D,f)
11. Methemoglobinemia. (D,o)
12. Urinary porphyrins ↑. (D,r)
13. May cause + L.E. test. (L,r)

Paraminosalicylic Acid

1. Urinary "glucose": Benedict's test +. (L,f)
2. Urinary urobilinogen ↑. (L,f)
3. Urinary porphobilinogen ↑. (L,f)
4. Test for phenothiazines in urine +. (L,f)
5. Serum cholesterol ↓ (if initially high). (D,f)
6. Coumarin anticoagulant effect ↑, prothrombin time ↑. (D,f)
7. ^{131}I uptake ↓, PBI ↓. (D,f)
8. May be hepatotoxic. (D,f)
9. May cause laboratory evidence of intestinal malabsorption. (D,f)
10. May be nephrotoxic. (D,o)
11. Serum K ↓. (D,f)
12. Acidosis. (D,f)
13. Urine discolored. (D,f)
14. May cause + L.E. test. (L,r)

Isoniazid

1. Urinary "glucose": Benedict's test +. (L,f)
2. May be hepatotoxic. (D,f)
3. Serum folate and B_{12} ↓ (biological assay). (D,f)
4. Direct Coomb's test positive. (L,f)
5. Coumarin anticoagulant effect ↑, prothrombin time ↑. (D,o)
6. May cause + L.E. test. (L,o)
7. Blood sugar ↑ and true glycosuria (high dose). (D,o)

Pyrazinamide and Ethionamide

1. May be hepatotoxic. (D,f)
2. Urinary 17-ketosteroids ↓ (pyrazinamide). (L,f)
3. Serum uric acid ↑ (pyrazinamide). (D,f)

Cycloserine

1. Serum folale ↓ (biological assay). (D,f)
2. May be hepatotoxic. (D,o)
3. May cause malabsorption syndrome. (D,o)

Rifampin

1. Coumarin anticoagulant effect ↓, prothrombin time ↓. (D,f)
2. Urine discolored red-orange. (D,f)
3. May be hepatotoxic. (D,o)
4. May be nephrotoxic: BUN ↑. (D,o)
5. Serum uric acid ↑. (D,r)

Capreomycin

1. May be nephrotoxic: BUN ↑. (D,o)
2. Serum K ↓, Mg ↓, Ca↓, alkalosis. (D,o)

Nitrofurans

1. Urinary "glucose": Benedict's test +. (L,f)
2. May be hepatotoxic. (D,r)
3. Urine discolored brown or yellow. (D,f)

Methenamine

1. Urinary catecholamines ↑; VMA ↑. (L,f)
2. 17-ketosteroids ↑, 17-hydroxysteroids ↑. (L,f)
3. Urinary urobilinogen alt. (L,f)
4. Urinary estrogens ↑. (L,f)
5. Pregnanediol ↑. (L,f)
6. 5-HIAA ↓. (L,f)
7. May be nephrotoxic (high doses). (D,o)

Nalidixic acid

1. Urinary "glucose": Benedict's test +. (L,f)
2. Coumarin anticoagulant effect ↑, prothrombin time ↑. (D,f)
3. Urinary 17-hydroxysteroids ↑. (L,f)
4. May be hepatotoxic. (D,o)

Amphotericin

1. Nephrotoxic. (D,f)
2. Serum K ↓, Mg ↓. (D,f)

Griseofulvin

1. Coumarin anticoagulant ↓, prothrombin time ↓. (D,f)
2. May be nephrotoxic. (D,o)
3. May cause + L.E. test. (L,r)
4. Urinary porphyrins ↑. (D,r)

at an estimated yearly cost of $3,000,000,000. Antibiotic complications account for a substantial proportion of this amount, and although there is some inevitability which we must accept, it is hoped that increased awareness of the various complications will help reduce the incidence of the problem.

Glossary of Abbreviations

d-ALA	*delta-aminolevulinic acid*
DNA	*deoxyribonucleic acid*
IGE	*gamma* E *immunoglobulin*
IGG	*gamma* G *immunoglobulin*
IGM	*gamma* M *immunoglobulin*
INH	*isonicotinic acid hydrazide*
RNA	*ribonucleic acid*
SLE	*systemic lupus erythematosus*

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MEDICAL STAFF CONFERENCE

The Nephritis of Systemic Lupus Erythematosus

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Dr. David W. Martin, Jr., Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

Dr. Sleisenger:* Systemic lupus erythematosus (SLE) is a disorder we see with surprising frequency here at the University of California, and the same appears to be the case with our close colleagues on the Peninsula at Stanford University. Today we have the distinct pleasure of having Dr. Halsted Holman here to give us his views about the pathogenesis and treatment of the nephritis of systemic lupus. As a prelude we have presented a recent case to Dr. Holman of a patient who has flagrant systemic lupus, which has been refractory to therapy. The patient had viral complications including herpes, and very severe progressive renal failure has developed; and the measures available to us seem quite limited.

Case History

The patient is a 19-year-old white man who was well until August 1969 when he developed generalized malaise, low grade fever, periorbital edema, polyarthralgias and peripheral arthritis, along with a scaly erythematous malar rash. He was noted by his personal physician to have proteinuria, microscopic hematuria and hyaline, granular and cellular casts in his urine. His hematocrit was 15 percent and on physical examination he had peripheral edema. He was first seen at our medical center in November 1969 when he was noted to have a positive lupus erythematosus test and a positive antinuclear antibody test. Direct Coombs' test was positive and he had light immunoglobulin chains in his urine. Renal biopsy at that time showed subacute glomerulonephritis with virus-like inclusions noted on electron microscopy. His BUN (blood urea nitrogen) was 73 mg per 100 ml and serum creatinine was 3.2 mg per 100 ml. His creatinine clearance was 34 ml per minute. He was treated with 125 mg prednisone daily and was discharged. He continued to improve and by June 1970 his creatinine clearance had increased to 100 ml per minute and his hematocrit was 35 percent. His serum complement levels had returned to normal. The steroids had been tapered by November 1970 to 15 mg daily. However, at that time he developed Raynaud's phenomenon and new arthralgias. His serum complement level dropped to less than 10 mg per 100 ml and his urinary excretion of light chains increased. The dose of glucocortico-steroids was increased to 30 mg daily, but by February 1971 his creatinine clearance had dropped to 83 ml per minute and he had 2+ pitting edema and 2+ proteinuria with marked microscopic hematuria. He was begun on furosemide (Lasix®). He was admitted for the second time to U.C. Medical Center in March 1971 after one week of cough which was productive of brownish sputum in the presence of fever and chills and occasional nausea and vomiting. He was found to have bilateral basilar infiltrates. His creatinine clearance was 56 ml per minute and fell to 23 ml per minute during the hospitalization in the presence of persistently elevated urinary light chain excretion. His serum complement level was depressed, and it was decided to add chlorambucil (Leukeran®) to his therapeutic regimen. He was discharged from the hospital on 2 April 1971, but his renal function continued to deteriorate despite the chlorambucil dose being raised to 8 mg daily. On 27 April 1971 he was readmitted because of a twenty pound weight gain since discharge and a creatinine clearance of 13 ml per minute. Since he was being considered for either anticoagulation therapy or renal transplantation, it was decided to obtain a renal biopsy to determine whether there were sufficient numbers of functional glomeruli present to justify an attempt at improving renal function by anticoagulation therapy.

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Throughout the patient's illness he had variable degrees of hypertension requiring 750 to 1000 mg of α-methyldopa (Aldomet®) daily for control.

Physical examination revealed a blood pressure of 165/92, temperature of 36.4°C (97.7°F), pulse 100 and regular and 18 respirations per minute. He had a Cushingoid appearance and was in no acute distress. There was present a diffuse erythematous macular rash over the malar area, ecchymoses at the venipuncture sites and benign-appearing fundi. The chest was clear to percussion and auscultation and the cor examination was unremarkable. He had good peripheral pulses. There was no abdominal organomegaly. There was mild scrotal edema and the extremities exhibited a bilateral 3+ pitting edema up to the knees.

Laboratory Data

Hematocrit was 21 percent, platelet count 93,000 per cu mm, 3.8 percent reticulocytosis, white blood cell count 7600 with 90 percent polymorphonuclear leukocytes and 2 percent bands. Sedimentation rate was 39 mm per hour. The prothrombin time was 10.1 seconds, partial thromboplastin time was 3.2 seconds and an activated clotting time was two minutes and five seconds. Serum electrolyte concentrations were sodium 133, potassium 4.8, chloride 102 and bicarbonate 21 mEq per liter. Serum calcium was 7.6 mg per 100 ml and phosphorus 5.0 mg per 100 ml. The serum creatinine was 5.0 per 100 ml, total serum protein was 4.5 gm per 100 ml with albumin 2.9 mg per 100 ml. Urinalysis demonstrated 2+ proteinuria with 50 to 100 red cells and 10 to 20 white blood cells per high power field. Electrocardiogram and chest x-ray were within normal limits.

On 6 May 1971 a renal biopsy of the left kidney was obtained. There was a severe vasculitis, fibrinous exudates in the tubules, and sclerosed glomeruli on histologic examination, and special staining techniques revealed deposition of IgC, fibrin and complement in the kidney glomeruli. On 9 April 1971 the patient developed a sudden retroperitoneal hemorrhage at the site of the kidney biopsy, went into a shock-like state, and required nephrectomy and splenectomy as emergency procedures. He had not been anticoagulated. Postoperatively, he developed a hemorrhagic pneumonitis of an unknown etiology. Following removal of the left kidney the renal function deteriorated to the extent that he required hemodialysis. On 10 June 1971, after considerable improvement, he developed an herpetic rash on his left leg requiring isolation and aggressive support care for two weeks. During the latter part of this hospitalization severe, uncontrollable hypertension developed which was treated with high doses of guanethidine (Ismelin®) and α-methyldopa (Aldomet). On 17 June 1971 the patient had several grand mal seizures in the presence of normal concentrations of electrolytes, blood gases, blood glucose, calcium and hematocrit. Lumbar puncture was unremarkable. The brain scan and EEG were normal. The patient was begun on diphenylhydantoin (Dilatin®) and had no subsequent seizures.

The patient was discharged 25 June 1971 feeling quite weak, but able to leave the hospital on his own. Serum complement was within the normal range and urinary light chain excretion was not detectable at the time of discharge.

Dr. Holman:† At one time I worked on topics like this. For the last year or more I have been an amateur accountant enmeshed in the tangle of medical school finances, and little else. In any event, along with *that* new aspect of medical education another is developing. We are turning our attention to the delivery of care to communities, and to problems of continuing education for health personnel. We on "The Farm" are involved with a network of hospitals in a continuing education program. I am delighted to be here to welcome the house staff of UC of San Francisco to the Continuing Education Program of Stanford Medical School.

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This patient is one of the unfortunate persons with systemic lupus erythematosus whose relentless disease from the outset represents one end of the clinical spectrum of SLE. The antithesis of this patient is the one with very mild disease who experiences perhaps transient rash or arthritis, mild anemia, and possibly other symptoms which persist for years and are accompanied by mild, if any, renal disease. In older days we recognized only patients like yours. More recently our understanding of immunological abnormalities and a quickening of our clinical perceptions have allowed us to recognize a broad range of clinical disease under the diagnosis of SLE. Serious illness and death are usually associated with nephropathy, encephalopathy or myocardiopathy.

SLE was one of the first illnesses in which autoantibodies were identified. It remains today the disease characterized by the largest number of autoantibodies. These autoantibodies react with many different constituents of the cell and are neither organ-specific nor species-specific. The reactive cell constituents include mitochondria, microsomes, the nuclear membrane, deoxyribonucleohistone, deoxyribonucleic acid (DNA), histone, nuclear ribonucleic acid (RNA), and at least one other soluble nuclear constituent. The autoantibody which reacts with deoxyribonucleohistone causes the formation of LE cells. These autoantibodies can be identified by a variety of immunological measures including complement fixation, hemagglutination and the fluorescent antibody method. With the latter method, different autoantibodies yield different patterns of nuclear staining.

When autoantibodies were first identified and shown capable of reacting with components of any cell, it was thought that they would be directly involved in cell damage. This was not confirmed, however, and there followed a period when the autoantibodies were considered byproducts of the disease process. Most recently, as immunological techniques have become more sensitive and immunological concepts more sophisticated, we have begun to identify ways in which autoantibodies do participate in pathogenic mechanisms. I shall talk today of these relationships and of their implications for clinical course, treatment and prognosis of the patient. Some of the newer perceptions are only in an emergent stage and many of my interpretations of the clinical data will, therefore, be speculative.

The critical contribution to our current understanding of the pathogenesis of lupus nephritis came from the experiments of Dixon and his colleagues.[1] They created conditions in which soluble antigen-antibody complexes appeared in the circulation of the animals and found that a nephritis developed which was indistinguishable from idiopathic glomerulonephritis in man. The antigen in question, bovine serum albumin (BSA), bore no known antigenic relationship to constituents of the glomerulus. In the glomerular lesions of the experimental rabbits were rabbit gamma globulin, bovine serum albumin and complement. Some of the rabbits did not form antibody to the BSA; they did not develop nephritis. Other rabbits formed large amounts of antibody promptly; they developed a transient glomerulitis with recovery. Those rabbits which demonstrated an intermediate antibody level, a situation conducive to formation of antigen-antibody complexes, developed the chronic nephritis.

You will recall that when increasing amounts of antigen are added *in vitro* to a constant amount of antibody there is an initial increase in the precipitate which is formed. As the amount of antigen is increased, a point is reached at which precipitate ceases to increase and then begins to disappear. The latter is known as the phase of antigen excess and is characterized by the presence of sufficient antigen molecules so that each of the two combining sites of each antibody molecule is combined with a single, unshared antigen molecule. An antibody molecule with two attached, unshared antigen molecules is a soluble complex. While no one has yet unequivocally demonstrated such soluble complexes in the circulation of experimental animals developing nephritis, the circumstantial evidence for their presence is very strong. In addition to the localization of antibody, antigen and complement in the glomerular lesion, there is also the evidence in experimental animals that the glomerular lesions can be reversed by diminishing the amount of antigen and thus reducing the propensity toward formation of soluble complexes.

During the period when this experimental model was developed and termed "immune complex nephritis," improved methods were found for measuring antibody to DNA in the serum of patients with SLE. This antibody was found in the serum of virtually every patient with lupus nephritis.[2] Immunopathological studies of glomeruli from these patients and isolation of gamma globulin from those glomeruli established the presence of autoantibody to DNA, DNA and complement in the glomerular lesions. While other types of autoantibodies were also eluted from such glomeruli, the relative concentration of the antibody to DNA in the glomerular eluates was much greater than that of the plasma which bathed the glomeruli. Simultaneously, better methods were developed for the detection of DNA in plasma, and it was found that many patients with lupus nephritis had apparently uncomplexed DNA in their circulation. It was also shown that the amount of antibody to DNA and the "free" DNA varied reciprocally in amount. This suggested that when significant antibody was present it combined with the DNA and the complex somehow left the serum.

Again, it has not been possible unequivocally to identify soluble complexes of DNA and antibody in the serums of patients with nephritis. Nonetheless, the evidence strongly suggests that lupus nephritis is an immune complex disease caused by that type of complex. Further indirect supporting evidence emerged from the demonstration that exactly the same circumstances obtained in the hybrid offspring of black and white New Zealand mice which commonly develop autoantibodies and a nephritis identical to that of SLE.

A more general role of immune complexes in diseases in man was indicated by the finding of antibody to streptococci and streptococcal antigens in glomeruli of patients with post streptococcal glomerulonephritis,[3] and by the demonstration that apparently soluble complexes of drugs and antibodies to the drugs could damage the membranes of such cells as platelets and red blood cells.[4]

The story is continuing to unfold. For example, one of the most perplexing questions has concerned the origin of the DNA in the serum of patients. Recently, various lines of indirect evidence have been advanced for the presence of a viral infection in SLE and the possibility that such an infection triggers the disease process in much the same way that streptococcal infection provokes rheumatic fever. A corollary would be the possibility that the DNA in the serum was of viral origin. Very recently it has become possible to isolate and begin the characterization of this DNA in serum. This work has been done by Dr. Dick Hunter working in our laboratory. The buoyant density of the DNA from SLE serum is different from that of normal human DNA. However, a similar DNA has been recovered from serums of normal individuals. Consequently, it now appears that DNA is commonly present in normal as well as SLE sera, though the amounts in SLE sera are greater. These studies are in their early stages, and it is not yet possible to state whether this serum DNA is a hitherto unrecognized form of normal human DNA or is a residue of past infections. The situation is reminiscent of the early days in the study of autoantibodies which were also found to be present in normal serum but in lesser amounts than in SLE serum.

Our methods of evaluation of patients with SLE have changed in parallel with the evolution of laboratory tests and of our conceptual understanding of pathogenesis of nephritis. We currently measure antibody to DNA, circulating DNA and serum complement in patient's serums. We make inferences from these measurements concerning the course and tempo of the disease. For example, the appearance of antibody to DNA or a rise in its titer, an increase in circulating DNA or a drop in serum complement are considered harbingers of deterioration in renal status. Conversely, improvement in these factors is thought to anticipate improvement in renal status. The true accuracy of these generalizations, however, has not been established. When the serological trends are accompanied by clinical trends in the same direction, operational conclusions are easy to draw. What remains uncertain is that true predictability of serological change before clinical change. Thus, it remains unsettled whether treatment should be keyed to serological change alone.

Corticosteroids provided the first effective treatment for SLE. Initially, they were used because of their anti-inflammatory capabilities, and they were well established as the primary mode of therapy before there was appreciable understanding of the immunological aspects of the disease. Currently, we make a more refined rationale for their use, namely, that they are both anti-inflammatory and immunosuppressive. At doses of prednisone approximating 1 mg per kg of body weight, a measurable immunosuppressive effect is obtained with diminution of both humoral and cellular responses. It is a pragmatic fact of clinical experience that this treatment will reverse the nephropathy of SLE in some patients. Responders are more commonly not azotemic; conversely, patients with measurable renal failure at the outset of treatment have a much poorer outlook.

Major problems with this treatment are ineffectiveness in some patients, and toxicity. Both are exemplified by your patient. After an initial response he apparently became refractory and has been on a relentless, though uneven, downhill course. I infer from the information provided that, despite clinical improvement, he never ceased to produce antibody to DNA, and presumably, therefore, continued to experience other immunological abnormalities. In this instance, therefore, immunosuppression with corticosteroids was at best partially effective.

It is settings such as this in which we now use cytotoxic drugs in addition to corticosteroids. Much clinical experience is accumulating which indicates that some patients who do not remit with steroid therapy alone will improve or remit when alkylating agents, purine antagonists or folic acid antagonists are added to the regimen. The full value of these drugs remains unknown. No well-controlled studies have yet been published which establish a true synergistic effect of cytotoxic drugs and corticosteroids. In some of the cases where benefit occurs, it is possible that the benefit is due to a cumulative use of steroids rather than to the addition of a cytotoxic drug. Furthermore, there are controlled studies using cytotoxic agents alone in untreated cases of SLE indicating that the drugs are either useless or much less effective than steroids. Nonetheless, it is probable that the combination of drugs is effective, and few patients are now allowed to die without being treated in that manner. It is interesting that the nephritis of New Zealand mice can be prevented or ameliorated with cytotoxic drugs alone. However, the drugs must be used in doses 10 to 100 times greater than the weight-related doses in man. This combination of drugs is also widely used to inhibit the rejection reaction against kidney and heart grafts in man. Here, too, the evidence suggests a beneficial effect of the combination as opposed to the drugs individually.

In lupus nephritis the clinical evidence suggests that the milder forms of disease will remit commonly with either steroid therapy or combination therapy.[5] For patients who are azotemic at the outset of treatment, the prognosis is much less favorable. In our experience more than 50 percent of the latter patients do not recover. The cause of death is either relentless progression of disease, or opportunistic infection, or both. Clearly, the use of heavy doses of anti-inflammatory or immunosuppressive agents, or both, seriously compromises the resistance of the recipient to infection. They experience unusual fungal, viral and protozoal infections. Your patient has had a herpetic lesion, which fortunately did not generalize.

"Innocent Bystander Injury"

The foregoing comments represent, in an oversimplified form, our current understanding of the main aspects of nephritis in SLE. Now I should like to extend some of this information beyond the kidney lesion. You are aware of the mechanism in certain drug reactions in which circulating erythrocytes, leukocytes, or platelets are damaged by soluble complexes of drug and antibody to drug. The reaction manifests itself as a hemolytic anemia, leukopenia or thrombocytopenia. Apparently, the soluble complexes have the capacity to attach to the membrane of the circulating cell and disrupt it. This is called "innocent bystander injury" because there is no known cross-reactivity between antigens of the cell membrane and the drug.

As immunofluorescent techniques have improved in sensitivity, it has been possible to demonstrate localization of human gamma globulin in many tissues of patients with SLE. For example, gamma globulin may be found around the basement membranes of both the dermis and the intima of small blood vessels. The antigen associated with this gamma globulin has not been identified.

Immune complex nephritis and the "innocent bystander" phenomenon suggest that circulating soluble immune complexes have an affinity for membranes. Should this also be found to be the basis for the immune globulin depositions in blood vessel walls, then it would be possible to ascribe a significant amount of non-renal tissue damage in SLE to the effects of immune complexes. It would not be surprising if complexes involving various autoantibodies and antigens were responsible for some of the nonglomerular lesions.

Your patient may have a number of circulating autoantibodies; this is suggested by the diffuse staining pattern in the fluorescent antibody test. While it is quite possible that his anemia and thrombocytopenia are a consequence of immunosuppression, they may also have a partial immunological basis. So may his seizures. Central nervous system disease is relatively common in SLE, yielding symptoms ranging from coma to focal signs including seizure disorders. In some instances, no morphological lesion can be found to explain the functional disorder; it is inferred that there is a subtle cellular encephalopathy. At other times a cerebral vasculitis is present. Immunofluorescent studies of brain lesions have been inadequate, and it is impossible to draw inferences concerning their genesis. However, complement levels in the cerebral spinal fluid are often quite low during lupus encephalopathy and appear to be independent of serum complement levels. Thus, the possibility of an "immune complex encephalopathy" remains open.

New Developments in Study of SLE

There are two recent developments in the study of SLE which have unusual potential significance. These concern the association of different clinical forms of SLE with different patterns of autoantibodies, and a possible genetic susceptibility to the disease. I should like to discuss them briefly before concluding on the question of utility of kidney transplantation in a patient such as yours.

An antibody is commonly found in SLE and related diseases which reacts with an extractable nuclear antigen (ENA) which is not DNA. This autoantibody is present in extraordinary titers, occasionally as high as 1:1,000,000 dilution of serum, in a particular clinical form of SLE.[6] The patients also have simultaneously certain clinical characteristics of SLE, scleroderma and polymyositis. They are characterized by a thickening of the skin, myositis, arthritis, striking adenopathy and Raynaud's phenomenon. Esophageal hypomotility is frequent. The skin lesions resemble those of typical scleroderma but with considerable intradermal edema. The patients rarely have nephritis, and antibody to DNA is uncommon. They are quite responsive to corticosteroids and the skin lesions commonly disappear, a result not encountered in progressive systemic sclerosis. In this group of patients the extractable nuclear antigen is sensitive to digestion with ribonuclease and trypsin, and is, therefore, presumably a ribonucleoprotein. In this subset of SLE the clinical features, the response to therapy and the prognosis appear to be different from those of SLE accompanied by classical lupus nephritis.

Among the patients with lupus nephritis who have antibody to DNA there is a group which also have antibody to ENA. In these patients the antigen is usually resistant to ribonuclease and is probably a different component of the nuclear extract. What is important is the fact that those patients with lupus nephritis who also have the antibody to ENA appear to have a higher incidence of spontaneous or therapeutic remissions than those who lack this antibody.[7] The mechanism of this different and better prognosis is unknown. An interesting possibility emerges, however, from *in vitro* studies. Mixing of DNA and its antibody results in a precipitate. However, if ENA is added at the outset, precipitation is inhibited. Whether the ENA blocks the antigen or the antibody is unknown. Furthermore, if isolated chromosomal material (deoxyribonucleohistone) is digested with deoxyribonuclease, ENA is liberated into the solution. It cannot be eluted without nuclease digestion. Thus, the ENA appears to have an affinity for DNA-histone. It is possible that the affinity is responsible for the *in vitro* inhibition of DNA with its antibody. It remains to be seen whether the seemingly protective effect of the presence of autoantibody to ENA in lupus nephritis is due to an underlying difference in the immunological abnormality of the patient, to circulating ENA interfering with the formation of soluble immune complexes

(ENA has never been demonstrated in the serum), or to a similar interference caused by the antibody to ENA. It is interesting that Gordon Sharp has demonstrated that infusion of the extractable nuclear antigen into New Zealand mice destined to develop lupus nephritis results in a postponing of the appearance of the nephritis and a lessening of its intensity.

Whatever the ultimate explanation of these various interactions, it is clear now that different clinical forms of SLE are associated with different patterns of autoantibody formation, that some of these clinical forms are more responsive to therapy than others, and that certain immunological abnormalities coincide with or result in an apparent protective effect for the patient. Thus, it is no longer possible to consider SLE to be a single entity and it is probable that the future will provide us with many ways of discriminating between types of SLE and hence inferring different prognoses and applying different patterns of treatment.

A genetic susceptibility to SLE has long been suggested by the appearance in families of more than one person with SLE, related rheumatic diseases, or illnesses characterized by immunoglobulin abnormalities. However, it has not been possible to demonstrate unequivocally an incidence greater than in matched controls of clinical disease or of serological abnormalities except hypergammaglobulinemia. A new approach has been taken to this question by exploring the frequency of particular histocompatability types in patients with SLE. Histocompatibility antigens are those components of the cell membrane which provoke the rejection reaction against a graft of foreign tissue. The precise structure of these antigens is controlled genetically in a way quite similar to blood group antigens, and the histocompatibility antigens can be typed in an analogous manner.

Grumet and his colleagues have demonstrated an unusual incidence of the HL-A8 and the w15 antigens in patients with SLE.[8] There is evidence of an association of other diseases in man with particular histocompatibility types. More important, it has been clearly demonstrated that the genes which control histocompatibility antigens also influence the capacity of an animal to form antibody. This is a very important discovery because it indicates a possible biological role for histocompatibility antigens. For example, they may function as a form of receptor site for antigen to combine with an immunocompetent cell to trigger antibody formation. What is most intriguing is the fact that the diseases which have been associated with different histocompatibility types are commonly characterized by immunological abnormalities. Thus, one could visualize a relationship between a genetically determined type of immune response and an increased susceptibility to diseases with immunological abnormalities.

It is too early to draw any specific conclusions about the genetics of SLE and related diseases. However, it is reasonable to contemplate a genetic influence not only on susceptibility to the disease, but also on the types of autoantibodies which arise. This would fit well with the emerging correlations between the patterns of immunological abnormality and the types of clinical symptoms. It would also be consistent with the clinical observation that patients with SLE often respond differently to the same mode of therapy. One can anticipate a situation a decade hence in which patients now clustered under the diagnosis of SLE will be recognized as belonging to one of a variety of genetic, biological and clinical subfractions, each with a different prognosis, a different need for therapy and a different appropriate therapy.

Kidney Transplantation

To return to your patient, he has widespread, serious renal disease which has been minimally responsive to medical therapy. Therefore, you are confronted with the question of kidney transplantation. Experience with transplanting in patients with lupus nephritis is not great. The few patients who have had transplantation appear to do roughly as well as patients with other forms of nephritis. Because they have a systemic disease, we must assume that the disease will ultimately affect the new kidney. However, there are certain favorable considerations. First, assuming the unavailability of a genetically identical donor, the medications used to suppress the rejection reaction of an allograft kidney are the same as those used to treat SLE. Second, if the transplantation can be done during relative quiescence of the SLE, the danger to the new kidney may be minimized. Third, while the experience with renal transplants between identical twins in situations in which the recipient had glomerular nephritis indicate that the new kidney is ultimately affected by the systemic disease, many years are necessary for that effect to appear. At the present rate of increase in our knowledge about SLE and our refinement of treatment measures, it is a fair expectation that medical management will be substantially better five to ten years from now. Thus, even if the transplanted kidney is affected, we may be able to manage that disease more effectively than we can now.

There may be some favorable signs with your patient. His complement level has recently risen and this may suggest a lessening of systemic disease activity. Furthermore, the amount of immunoglobulin light chains in his urine has diminished. While either or both of these developments could reflect further reduction in glomerular infiltration alone, they also might represent an amelioration of the disease process. If the latter were true, the outlook for a successful transplantation would be better.

Fifteen years ago we could not deal effectively with patients such as yours. We treated them primarily symptomatically, and they died. Today we treat them vigorously and are having partial success. The vigorous treatment creates additional problems. Tomorrow, with the current explosive growth in our knowledge of the disease process and the beginning of establishment of a rational basis for therapy, we may expect that our clinical capabilities will be substantially improved. It is not unreasonable to hope that before our practicing lifetimes have run their course we can approach such patients with an accurate understanding of the basis of their disease, and with methods of therapy which are no longer pragmatic but are designed specifically to terminate the disease process.

TRADE AND GENERIC NAMES OF DRUGS

Aldomet®	α-methyldopa
Leukeran®	chlorambucil
Ismelin®	guanethidine
Dilantin®	diphenylhydantoin
Lasix®	furosemide

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ONE-A-DAY INSULIN IS "PHYSIOLOGICALLY WRONG"

Most diabetics taking insulin can't be treated with just one shot of long-acting insulin a day. It's physiologically wrong because the body gives many squirts of short-acting insulin. Until people in the medical profession realize that, we're going to have the same old "shot" diabetics at the age of 45 or 50—blind, with kidney disease, and so forth—because of two things. First, you don't treat diabetes by dietary restrictions at any time, except in fat people. Second, you don't give just one shot of insulin once the patient has to take more than 30 units a day. It just can't be done. You've got to give two, and usually mixtures. Then if that's done for the next 20 years, you're going to have a totally different diabetic population under treatment.

—FROM PANEL DISCUSSION ON THE TREATMENT OF LATENT AND SUSPECTED DIABETES
Extracted from *Audio-Digest Internal Medicine,* Vol. 17, No. 9, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

Important Advances in Clinical Medicine

Epitomes of Progress -- Neurology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Neurology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 693 Sutter Street, San Francisco, Ca. 94102.

Bloody Tap and Yellow Peril

BLOODY CEREBROSPINAL FLUID (CSF) sometimes poses a problem to the clinician trying to assess the probability of an intracranial hemorrhage, whatever the pathological source. It is commonly known that clearing of the blood from the second and third tubes suggests traumatic technique (usually from puncture of the *anterior* epidural vessels). It is not so commonly known, however, that even should clearing not occur, there are further steps which can differentiate quickly between a spontaneous or pathologic hemorrhage which occurred more than 4 to 12 hours before to lumbar puncture and traumatic puncture technique. Those steps are to centrifuge the CSF (an ordinary centrifuge designed for urine and blood work is adequate) and examine the supernatant for bilirubin and protein. Xanthochromia of the supernatant CSF with protein less than 200 mg per 100 ml may be construed as proof of hemorrhage more than 4 to 12 hours previously. If bilirubin is shown to be present by Ictotest or other appropriate technique (the tests otherwise used for urine are acceptable), then hemorrhage has been proved regardless of the protein level. Even in a jaundiced patient, this test is of value since conjugated bilirubin does not cross the intact blood brain barrier. Purists may wish to show that the CSF bilirubin concentration exceeds at least that of serum unconjugated bilirubin.

If the supernatant CSF is red or orange, it is still possible that bilirubin may be demonstrated by appropriate chemical tests to prove previous hemorrhage. Unfortunately, the demonstration of early products of hemolysis is of little or no value in differentiating hemorrhage from traumatic technique, since hemolysis often starts in the needle.

The presence of crenation in the red cells present in uncentrifuged spinal fluid is of no diagnostic importance because spinal fluid is normally slightly hypertonic compared with serum. Red cell crenation can occur within minutes in the CSF.

Finally, it is worth mentioning that the presence of bilirubin in the CSF may prove the occurrence of a hemorrhage up to three weeks before examination—long after the blood cells and earlier hemoglobin breakdown products have cleared.

LEONARD J. GOSINK, M.D.

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Subacute Sclerosing Panencephalitis

SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE) is a chronic progressive disease of the central nervous system primarily affecting children of school age. The clinical course can be divided into three stages manifested by behavioral disturbance, dementia, myoclonus and incoordination and ultimately amentia and decerebrate rigidity. Laboratory studies are normal except for an elevated cerebrospinal fluid (CSF) gamma globulin, and the electroencephalogram is characterized by low voltage, slow irregular background activity with paroxysmal bursts of generalized bilaterally synchronous high voltage, slow and sharp waves. Following Connolly's observation that three patients with SSPE had high antibody titers to measles, other laboratories confirmed that elevated serum and CSF measles antibody titers and specific measles immunofluorescence of brain cells were seen in patients with SSPE. Further, paramyxovirus-like particles were demonstrated by electronmicroscopy in brain biopsy of these patients. More recently, the measles virus has been isolated from brain biopsy specimens and lymph nodes of patients with SSPE, suggesting that there has been a suppressed measles infection. Thus far no therapeutic agent has been found to be effective in halting or reversing the disease process. The effects of Transfer-Factor administration are yet to be evaluated.

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Current Trends in L-Dopa Therapy of Parkinsonism

L-DOPA HAS PROVED to be the most effective treatment available for parkinsonism and is helpful in more than 70 percent of patients. Although relatively little serious toxicity is produced by this drug, almost all patients experience some uncomfortable side effects. Fortunately these seldom necessitate discontinuing the drug, but in about 10 percent of patients intolerance is great enough to prevent use of an optimal dose. Common side effects include gastrointestinal distress (often with vomiting), postural hypotension, impaired cerebration and abnormal involuntary movements. Careful adjustment of dosage and taking each dose with food will often decrease the side effects.

Dopamine, a neurotransmitter of which L-dopa is a precursor, is the substance which is effective against parkinsonism but it does not cross the blood brain barrier well enough to be useful either orally or parentally. For the same reason dopamine formed in the body outside the brain will not be effective. L-dopa, however, is able to enter the brain, where it is converted to dopamine. Decreasing the formation of peripheral dopamine with a dopa-decarboxylase inhibitor such as alpha-methyldopahydrazine, which is also unable to cross the blood brain barrier, allows a larger proportion of the circulating L-dopa to be utilized by the brain in the formation of dopamine. This more efficient utilization of L-dopa permits the use of much smaller doses, which decreases the gastrointestinal distress but does not appreciably diminish the other side effects. Although the dopa-decarboxylases are available at present only for experimental use, the apparent absence of severe toxicity makes it likely that they will be released soon for general use.

Long term maintenance on L-dopa although not usually resulting in decreased control of the symptoms of parkinsonism, may cause the appearance of additional evidences of intolerance. These differ slightly from the side effects occurring early and include abnormal involuntary movements, impairment of cerebration and episodic loss of muscle tone so great and sudden that the patient may fall. Management of these complications requires reduction of the dosage, although frequently the symptoms will reappear after a time at the lower dosage. Discontinuing the drug may be necessary. Although difficult to confirm statistically, it appears that in some cases L-dopa slows or prevents the usual progression of Parkinson's disease.

In summary, L-dopa is very effective in alleviating most of the symptoms of parkinsonism, but its use requires careful adjustment of dosage and close observation of the patient. The use of L-dopa in the treatment of other movement disorders has been, in general, disappointing.

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Alpha Rhythms and What They Mean

THE ALPHA RHYTHM is to the brain what the electrocardiogram is to the heart. However, while we know the significance of the latter rather precisely, that of the alpha rhythm remains an enigma. Nevertheless, alpha rhythms (there is one for each hemisphere) are very useful in electroencephalogram diagnosis since they reflect maturational processes and tend to be suppressed by mass lesions such as tumors.

The alpha rhythm closely reflects the state of consciousness and there has recently been great interest in rendering it audible by special electronic monitors. In listening to this alpha rhythm, a subject completes a feedback loop (bio-feedback) and can learn to enhance or suppress this activity. Some have claimed that the process of feedback enhancement represents a special state of consciousness related to meditative experience. There are some indications that these induced states may have therapeutic value in reducing anxiety and tension.

Computer analysis of the alpha rhythm has recently revealed the presence of many unsuspected components in what was formerly regarded as a trivial ten cycle sine wave. These newly demonstrated alpha components may contain information which will provide further insight into brain function.

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Myasthenia Gravis

DESPITE THE FACT that the conventional anticholinesterase medications such as neostigmine methylsulfate (Prostigmin®), pyridostigmine bromide (Mestinon®), and ambenonium chloride (Mytelase®) continue to be widely used in the management of myasthenia gravis, other modes of therapy must be considered.

It has been shown recently that patients who are relatively refractory to anti-cholinesterase drugs or who cannot tolerate them may respond dramatically to high doses of prednisone (100 mg) administered on alternate days. While the patient is receiving steroids, all forms of anticholinesterase medication must be withheld and the patient must be carefully monitored for possible complications of the disease and steroid therapy. The latter are generally minimized by the alternate day regimen. Since some patients may actually worsen transiently at the initiation of steroid therapy, vital functions must be carefully monitored and the initial treatment must be carried out in the hospital.

Until recently, thymectomy for myasthenia gravis was advocated for patients who had either evidence of thymoma or for female patients under age 30 who have had the disease for less than five years. Long-term follow-up studies published recently suggest that patients of all age groups and both sexes benefit from thymectomy irrespective of the duration of the illness. Long-term follow-up studies indicate that progressive improvement following thymectomy occurs in up to 75 percent of cases. There appears to be good correlation between improvement and certain quantitative histologic abnormalities observed in the thymus. Patients with the least amount of germinal proliferation of the thymus tend to improve most rapidly.

Once diagnosis is properly established, the patient should be given the benefit of conventional therapy. Should this fail, alternate day steroid therapy or thymectomy should be considered.

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Treatment of Multiple Sclerosis

The cause of multiple sclerosis (ms) remains obscure and there is no specific therapy. While steroids have been advocated, there is little substantive research evidence to endorse uncontrolled use of these agents.

A recently completed national cooperative study on the use of acth in ms during acute exacerbations revealed a slightly beneficial effect: During four weeks of observation, which included only two weeks of acth, a slightly greater number of patients improved slightly faster than those in the placebo group. Similar reports of beneficial short-term treatment for acute symptoms, especially for acute optic neuritis, have been published. There is no convincing evidence for the value of long-term maintenance with steroids.

As a practical guide, acth or oral steroids can be given in a tapered dose over the course of four to six weeks. Since the improvement following steroids usually occurs within the first 72 hours, there appears little to be gained by continuing treatment longer.

As there is some evidence that an immune response is a factor, immunosuppressive therapy has recently been in vogue as a treatment for this disease but the results have been inconclusive and in general disappointing.

Patients with this disease should be kept under observation, however, for there are beneficial measures that can be taken—physical therapy for gait training, stretching and strengthening exercises for spastic weakness and the use of ice packs for spasticity. Patients should be encouraged and pushed to be as physically active as possible.

As adjuncts, anticholinergic agents such as ProBanthine® (propantheline bromide, U.S.P.) can be helpful in controlling bladder and bowel spasms and in relieving the embarrassment of urinary urgency and incontinence. In addition, patients should be on a well-balanced dietary program. Vitamins can be added as a supplement.

Prompt attention to infections, be they of the skin, urinary or respiratory systems, and in general the treatment of any physical ailments are especially important to patients already beset by an underlying neurological disease.

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New Diagnostic and Treatment Techniques in Cryptococcal Meningitis

Positive cerebrospinal fluid latex agglutination of cryptococcal antigen was found in patients with chronic meningitis not diagnosable by India ink preparations or cultures of the cerebrospinal fluid. To date, the latex agglutination technique appears more sensitive than the complement fixation test for the detection of cryptococcal antigen in the cerebrospinal fluid. A false positive reaction may appear in the serum latex agglutination cryptococcal antigen test due to the presence of circulating rheumatoid factor in the serum, but this does not occur in testing the cerebrospinal fluid. The Communicable Disease Center in Atlanta has been able to perform the cerebrospinal fluid latex agglutination cryptococcal antigen test on patients suspected of cryptococcal meningitis.

Before the introduction of amphotericin B in 1956, cryptococcal meningitis was almost invariably fatal. Now, in approximately two-thirds of patients this agent can eradicate the organism from the spinal fluid. Initially, 1 mg of the drug is diluted in 5 percent glucose in water and administered intravenously. The dosage is rapidly increased to deliver 1.0 to 1.5 mg per kg of body weight per day, although it is unusual to exceed 50 mg a day. Side effects include headaches, chills, fever, and vomiting in addition to potentially non-reversible renal damage which is directly related to the total dosage. Frequent monitoring of the urine, hemoglobin, serum creatinine, and blood urea nitrogen is mandatory. A therapeutic end-point is rarely sharply delineated and treatment is generally continued to deliver a total of 2,000 to 2,500 mg in six weeks to four months. Intrathecal therapy is reserved for the critically ill or patients in relapse.

Since the first report of its effectiveness in cryptococcal meningitis in 1967, 5-flurocytosine (5-FC), has been shown to be an important adjunct to amphotericin B as well as an agent for primary treatment. In contrast to amphotericin B the drug is given orally and its side-effects are minimal. These include a mild and apparently reversible anemia and elevation of the serum glutamic-oxalacetic transaminase. The recommended dosage is 150 mg per kg of body weight per day divided into six-hour intervals. The eradication rate is unknown, due to limited reports of the drug, but as a primary therapy it is probably somewhat less effective than amphotericin B. Combined use of the drugs has been cited in case reports, but it remains uncertain if the combination is more or less effective than either drug alone. As with amphotericin B, no practical end-point of treatment can be stated.

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The Use of AMICAR® in Subarachnoid Hemorrhage

There is widespread controversy about the optimal time for surgical intervention after subarachnoid hemorrhage secondary to ruptured intracranial aneurysms. The risk of early recurrent bleeding is often a major consideration in determining the appropriate time for operation. Recently attempts have been made to tide the patient over the early critical days by using epsilon amino caproic acid (AMICAR®) to prevent clot lysis and recurrent hemorrhage.

Amicar is a synthetic monoamino carboxylic acid that is a competitive inhibitor of plasminogen (profibrinolysin) activators. It also inhibits plasmin (fibrinolysin) but to a lesser degree. Therefore it prevents formation of plasmin which is responsible for the destruction of fibrinogen, fibrin and other clotting components. Thus it inhibits the dissolution of clots, but conversely may exaggerate thrombotic tendencies.

It has been used to control hemorrhage during cardiac and thoracic operations, portacaval shunting, abruptio placentae and in the "fibrinolytic bleeding" associated with metastatic prostatic carcinoma and leukemia.

In preliminary neurosurgical reports, Mullan and Dawley noted recurrent hemorrhages in only two of thirty-five patients with subarachnoid bleeding who had received AMICAR. Norlen and

Thulin reported similar good effects, as have Nibbelink and Jacobsen. The latter used the streptokinase clot lysis determination to monitor their patients. The drug is usually given intravenously at one or two-hour intervals to a total daily dose up to 30 grams. Close hematological consultation is advised. Cardiac and hepatic necrosis as well as massive intrarenal clotting with anuria are among the more serious complications reported. At present the use of the drug should probably be restricted to those centers where adequate control series can be studied under close hematological as well as neurological supervision.

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Headache and "The Pill"

THAT HORMONES INFLUENCE migraine headaches has long been known. Increased migraine headaches during or just before menstruation and freedom from migraines during pregnancy are common observations. Since the advent of oral contraceptives, it has been noted that pre-existing migraine headaches may be aggravated in some women and ameliorated in others. Changing the type of contraceptive drug may reduce or increase the headache problem. Migraine headaches may occur for the first time after initiation of oral contraceptives. In any of these situations it is difficult to distinguish to what degree the effects of "the pill" are psychological and to what degree pharmacologic in the alteration of the headache pattern.

Although universal agreement on the subject is lacking, there is probably a very slightly increased incidence of thrombotic cerebral vascular disease in women using oral contraceptives. Some authorities believe these drugs may cause an increased risk of stroke in women with a migraine tendency, but as yet there is no conclusive proof of this belief.

Our present knowledge suggests that a history of migraine headaches should not be a contraindication to oral contraceptives. Should pre-existing migraine worsen or migraine headaches appear for the first time, a trial of a different drug, perhaps with less estrogen, should be considered. In an occasional woman, the severity of the headache problem will preclude continuing use of these drugs. Oral contraceptives should be stopped immediately in any women, with or without headache, who begins to have episodes of neurologic dysfunction indicative of transient cerebral ischemia.

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The Medical Treatment of Epilepsy

THE MEDICAL TREATMENT OF EPILEPSY is limited to drug therapy, elimination of medical cause, when possible and helping the patient to accept, understand his illness.

Before drug therapy can be started, the type of epilepsy should be established since choice of drug is often dependent on the type of epilepsy.

One should be alert to possible metabolic disorders in infants and young children, while brain tumors should be suspected when seizures occur for the first time after age 25.

Choice of drug depends primarily on the type of seizure., Diphenylhydantoin (Dilantin®) with or without phenobarbital or mephobarbital (Mebaral®) is the drug of choice in grand mal, psychomotor, and focal seizures. Primidone (Mysoline®) alone or with diphenylhydantoin is also effective in these seizures. Ethosuxmide (Zarontin®), paramethadione (Paradione®), and trimethadione (Tridione®) are the most effective drugs in petit mal seizures. Since the latter two drugs are rather toxic and may exacerbate grand mal seizures, mephobarbital should also be given when they are used. Dosages of the above listed drugs depend on the age and weight of the patient and most can be taken on a two to four times daily schedule. The most common cause of drug failure in epilepsy is inadequate intake of drug, which may be due to improper prescribing by the physician or failure of the patient to take the prescribed amount of drug.

Most important in the treatment of epilepsy is a continued and careful follow-up of the patient's progress. The follow-up visit should be used to evaluate the patient for evidence of drug toxicity or signs of progressive neurologic disease. Attention should be given to the patient's emotional state and needs. Interval blood counts and urinalysis should be done. If the patient is not adequately controlled or shows drug toxicity on what the physician considered adequate dosage, serum levels for Dilantin (sodium diphenylhydantoin) and barbiturates should be obtained. These can be obtained in most laboratories. Dilantin therapeutic levels run 10 to 20 ppm, barbiturates between 10 and 15 ppm. However, lesser amounts or greater amounts should alert the physician to investigate the patient's intake of the drugs.

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Propranolol in Neurology

Propranolol (Inderal®, Ayerst) is a beta-adrenergic blocking drug which is frequently useful in prophylaxis against migraine and in the treatment of tremor. Its mechanism of action in these disorders is not yet understood. The drug is extremely safe when the published contraindications are borne in mind and it is coming into general use by the neurological community.

The effective dosage for migraine prevention is commonly 20 mg, four times daily, but it is likely that higher doses may be necessary.

The effective dosage for essential (or familial, or senile) tremor has often been as high as 120 to 240 mg daily. Although some patients benefit strikingly and others not at all, some of the reported failures have been in patients taking low doses. Parkinsonian tremor seems to respond less well to this drug, though it has often been beneficial even in this condition.

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Graduate Medical Education

GRADUATE MEDICAL EDUCATION has come to represent a significant segment of both medical education and medical practice in the United States. It is estimated that interns, residents and clinical fellows, commonly known as house staff or house officers, now render something like 25 percent of all the medical care which is given. They are considerably more numerous than medical students and they make up a substantial proportion of the total number of physicians who provide patient care. A large portion of the resources available for medical care is consumed by these programs and their cost is beginning to be of some concern to the public.

It is during his graduate medical education that a young physician learns of the capabilities and limitations of modern medical science by precept and by experience. As an undergraduate medical student he is an observer; as an intern, resident or clinical fellow he participates in patient care, assuming gradually greater responsibility; and then in active practice he finally has the full responsibility. Thus graduate medical education is a transitional period between the role of observer and the full responsibility of active practice. As an aftermath of the Flexner Report in 1910 and the subsequent growth and development of science in medical education, specialties are proliferating (general practice and family practice are now regarded as specialties), and graduate medical education is generally carried on within the framework of the specialties, and training is pointed toward the requirements of the specialty boards for certification in the specialty.

In the last decade a number of forces have appeared which are beginning to complicate things in graduate medical education. There has been a reaction against too much specialization in medicine and a resurgence of professional and public interest in primary care and family practice. A maldistribution of physicians, both geographically and by specialty, has raised serious questions concerning what should be the goals of graduate medical education. There are complaints that there are too many specialists, particularly in those specialties where the fees are higher, and that this over-supply and under-use tends to keep these fees up. There is a revolt against the use of the poor as clinic patients and "teaching material" anywhere in medical education. One level of high quality care for all is a clear intent of the law. This has given rise to many problems in the house officer training situation which are at present unresolved. But by far the most important new force in graduate medical education is rising costs and how they are to be paid. Interns and residents have been very aggressive and very successful in forcing improvements in their pay and working conditions. In California these salaries are now in the order of $9,000 to $18,000 a year. This, coupled with the fact that graduate medical education requires that many specialties and expensive specialized facilities be available in a high quality program if there is to be an acceptable learning experience, now has placed the cost of a good program beyond what can be supported by traditional means. A serious situation exists.

The problems of graduate medical education are thus not simple. How they are dealt with now will no doubt determine the quality of the scientific and technologic medical care Americans will receive in the years ahead, since this can only be as good as the training their physicians have received. At the present moment it seems as though there is "no way" to deal with many of these problems. But some sort of start should be made. It is therefore suggested that the time has come for certain issues to be faced squarely:

¶ *Graduate medical education should take place only in those settings where a certain critical mass of specialties and specialized facilities are to be found,* since it is essential that all physicians learn the capabilities and limitations of modern medical science and technology during this period of their preparation for practice whether it will be in such centers or elsewhere. Decentralized on-the-job training in limited practice situations cannot be substituted for active participation in broadly based learning experience with scientific medicine at its best.

¶ *The matter of who is responsible and who is rendering services to an individual patient in the graduate medical education setting needs to be clarified.* Graduate medical education is that segment of a physician's training between medical school where he has no responsibility and active practice where he has full responsibility. During this period the young physician must assume increasing decision making and practice responsibility as part of his training, and in so doing it turns out that he actually delivers approximately 25 percent of all the medical care given in the nation. Yet just who to be held responsible to the patient for what or who should be paid for what is not as clear as it should be.

¶ *The need for better distribution of physicians among the specialties including family practice must be satisfied.* Here the needs of a major medical center for a distribution of specialties for a balanced program of graduate medical education and the tertiary care the above render are quite different from the distribution or balance which is desirable in an urban or rural practice situation where the emphasis is on primary and secondary care. This disparity is to a considerable extent responsible for the present maldistribution of specialties in practice and it should have considerably more study and attention.

¶ *There is a clear need for more realistic financing of graduate medical education.* The costs are substantial and are increasing. They can no longer be borne by the sick patient who happens to be in a hospital with a fully developed house staff. So far the private sector has found no adequate solution for this; and if it does not, there will be increased public funding, and with it increased bureaucratic and political control of what is taught, where it is taught, to whom it is taught and all that this entails.

The enormity and implications of all these problems in graduate medical education are not generally realized, nor is their complexity, nor is the awkwardness of the organizational mechanisms we have for dealing with them. Quite recently a Liaison Committee on Graduate Medical Education has come into being, sponsored by the American Medical Association, the American Board of Medical Specialties, the Association of American Medical Colleges, the Council on Medical Specialty Societies and the American Hospital Association. It has representation from each of these organizations and one representative from the public and one from the federal government. Its thrust is to be in the field of accreditation of graduate medical education and specialty training where the problems are great and it is possible that such a liaison committee can be effective.

But the sad truth is that there is as yet no recognizable mechanism to deal constructively with the problems of graduate medical education herein described, from the standpoint of the needs of practice situations, of educational institutions, or of the growing public concern with the educational product, and with the need for adequate resources, financial and otherwise, for graduate medical education.

The initiative is up for grabs.

—MSMW

Antimicrobial Drugs and Adverse Drug Reactions

TWENTY TO FORTY PERCENT OF PATIENTS treated in hospitals receive at least one antibiotic, and a significant proportion of them receive two or more. The frequency of use of antimicrobials in the treatment outside hospitals probably is less, but these agents are now and will continue to represent a large proportion of the drugs prescribed by physicians.

An increasing number of new antimicrobial drugs have become available yearly and are added annually to the large number already available. This number is magnified by the variety of different products with different names but representing the same drugs. For example, there are at least 37 different tetracycline products available and each is often marketed as having attributes more advantageous than others.

Antimicrobial drugs certainly have important therapeutic functions when used for treatment of characterized and defined infections. Too often, however, they are prescribed unwisely and without justification. Infections by a few specific microorganisms can be prevented by prophylactic use of particular antimicrobial drugs, but antibiotics are not effective in preventing infection in general, and when used for such purposes more often increase the risk of infection, particularly by antibiotic resistant microorganisms. Physicians also may prescribe antibiotics when clinical discrimination is imprecise, and these drugs are used to "avoid overlooking an infection and failing to treat it." There are circumstances when empiric antibiotic treatment is justified but more often such treatment is unwise.

The desirable dosage of antimicrobial drugs used to treat patients usually is well known or readily determined. Occasionally, however, antibiotics may be given in too low a dosage, and this may be attributed to their high cost. More often, however, physicians prescribe too large a dose of an antibiotic, particularly if the patient seems very ill. The route of administration may require alteration if a patient is severely ill, particularly if in shock, but the effectiveness of antibiotics is not increased once a dosage has been given which will kill the microorganism or terminate its replication. Bacteria killed with one microgram of an antibiotic will not be killed further with ten micrograms. There is no need to kill a fly with a hammer if a fly-swatter will do. The hammer may in fact cause damage to the fly's host. Similarly, an excessive dose of drug increases the risk of damaging the patient. These comments are also appropriate to the duration of treatment. Once flies have been killed other means than the fly-swatter or hammer must be used to remove their remains and repair the damage they may have caused. Antibiotic treatment may not, and does not, compensate completely for defective host resistance and repair.

The predictability and prevention of adverse drug reactions are related to familiarity with the risks and circumstances responsible for their occurrence. Typhoid fever, for example, will occur unpredictably and will not be prevented if water or food contamination and the typhoid carrier are not recognized as determinants. There are many different determinants of adverse drug reactions. Many are related to particular types of drugs, while other determinants are more generally applicable. The pharmacologic and clinical determinants of adverse drug reactions are discussed in a Specialty Conference on Complications of Antibiotic Therapy which appears elsewhere in these pages. Therefore, only some of the generally important means for their prevention or control will be presented here. Nevertheless, the judicious but restrained use of antibiotics is of primary importance.

Adverse reactions to drugs have become a major public health problem. Estimates have suggested that in the United States several hundred thousand persons a year enter hospitals for drug-induced diseases. The untoward drug effects occurring in ambulatory and hospitalized patients must be added to this number, which emphasizes the magnitude of the difficulty and need for concern.

No drug, including antimicrobial agents, is completely safe, but the reasons why some persons are predisposed to adverse drug effects are incompletely understood. Genetic, metabolic and other determinants are known to be responsible for some drug-induced illnesses, but the determinants of most untoward drug reactions are not known.

Two manipulatable and identifiable determinants of adverse drug reactions are the number of drugs administered to a patient and a previous history of a drug-induced illness. As the number of drugs given to a patient is increased, there is a progressive increase in the risk of an adverse drug reaction. In part, this effect is additive but it is also attributable to potential adverse drug interactions. The probability of drug interaction as a potential cause of untoward effects may be as high as 50 percent in ambulatory patients. This risk is increased as the number of prescribers increases. Avoidance of this risk is dependent upon the physician's being aware of all medications being taken by a patient, not just those personally prescribed.

Patients admitted to the hospital with a drug-induced disease are three times more likely to have an adverse reaction to another drug during hospitalization. Similarly, patients with a past history of a drug-induced illness are predisposed to additional ones. Repetitive adverse drug reactions are common. Recognition of a drug-induced disease in a patient, therefore, requires added caution in drug prescribing.

Avoidance or prevention of all drug-induced disease is not possible. New, previously unrecognized reactions to old drugs are being described, and new drugs are always a potential source of new reactions. Scrutiny of prescribing practices and of medications taken by patients, careful use of drugs in predisposed patients, and avoidance of excessive drug prescribing are the methods which, diligently followed, can reduce the problems of drug-induced disease.

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AMPAC–CALPAC

As this is written the results of the November 7 state and national elections are not known, and as this is read they likely will be. Hence this is a good time for an objective comment or two about AMPAC and CALPAC.

For some years now these political action committees have been sponsored at the national level (AMPAC) by the American Medical Association and at the state (CALPAC) by the California Medical Association. They have gradually increased in membership and in recent years their dollar contributions to the candidates selected for support have been large enough to be both helpful to the campaign and appreciated by the candidates. Further, we are informed that AMPAC and CALPAC are now able to hold their own at both state and national level with the best of the political action committees no matter whose they are.

It may be of interest to many to know that in the primary election last June and in this November election a total of 136 candidates were supported in California, and the breakdown shows that 74 of them (54%) were Republicans and 62 (46%) were Democrats. Thus any doubts that CALPAC is not bipartisan should be allayed. Since it has become abundantly clear that medicine has problems with government no matter which party is in power, it has become clear also that it is to the advantage of medicine and better medical care, that persons be elected from both parties who are well informed and understand the problems of health care.

It is equally of interest and worth emphasizing that many organizations of diverse and often opposing interests have political action committees which support and then claim the support of candidates after they have been elected to public office. It is naive to assume that many candidates supported by AMPAC or CALPAC are not also supported, and perhaps often better supported, by interests with other views than those of medicine. So it is also naive to assume for one moment that any candidate supported from out of our pockets is henceforth to be counted as in our pockets. However, we can expect to get the ear of candidates we support. But in the long run those in public office are far more influenced by public opinion than anything else, even including money, because that is where the votes are. Political action committees are important but alone they are not enough, and this truth should never be forgotten.

AMPAC and CALPAC have placed medicine in the big leagues as far as this particular form of political persuasion is concerned, and for this the profession is much in their debt. They have by no means yet reached their full potential for influence and effectiveness. They merit the continued financial support of individual members of the profession and the far more active participation of their own members in their councils and decision-making processes.

—MSMW

Special Editorial

Some Planning Suggestions In Cancer Care

THE TRADITIONAL INSTITUTIONAL practice patterns make it difficult to accommodate the complex nature of cancer therapy and efforts toward a regional assessment of the cancer problem are greatly needed. These efforts should take into consideration resources in the community for detection and diagnosis, a focus for pretreatment planning through establishment of interdisciplinary channels between primary physicians and surgeons, radiotherapists and chemotherapists, and a recognition and definition of the role of each of these oncologists, particularly the medical oncologist.

Consideration must be given to the expertise and capacity of local facilities to provide adequate treatment and not merely palliation. Particular concern must be directed to radiation therapy facilities because of shortage of personnel and high cost of equipment. A coordinated cancer treatment system will recognize that it is neither possible nor desirable to treat all patients in teaching centers. Cooperation between the private sector and universities is essential to expanding and improving clinical research and to augment training programs for cancer workers. Better organization and support of regional planning are essential to promote these concepts.

Recommendations for Treatment Facilities

In order to make feasible a coordinated system, four types of facilities are suggested, each having a specific function but cooperating in various ways to provide for the cancer management needs of a given geographical region. The four treatment facilities are:

1. Comprehensive Oncology Center
2. Clinical Oncology Center
3. Correlated Oncology Unit
4. Urban Treatment Unit

The Comprehensive Oncology Center is a complete treatment facility, providing representation for surgery, radiotherapy, and chemotherapy. Usually the unit would be located within a university medical center, but there is nothing to preclude its location within or adjacent to a community medical institution. Surgical services would be provided through a consultative staff with the various surgical subspecialties represented, and a surgical oncologist could be a full-time member of the professional group, serving as a consultation resource for other surgeons. Radiotherapists and chemotherapists would be members of the full-time staff.

The center should serve a minimum of 400,000 people, since at least 75 patients a day in radiotherapy should be anticipated to warrant establishing it. Community leadership in encouraging early detection principles among primary physicians would be provided. A full range of diagnostic and treatment facilities would be available, and supportive services in related fields would be provided or encouraged.

In addition to the broad range of clinical services, including clinical radiophysics and active clinical research, the Comprehensive Oncology Center would have an intrinsic training program in oncology. Basic cancer research would be conducted through relationships established with related departments in such areas as virology, immunology, radiobiology and cellular biology.

* * *

A Clinical Oncology Center would have all the clinical and treatment capabilities of a Comprehensive Center, but would not have intrinsic residency training nor basic research activities. Physics would be available at the same clinical level as in the Comprehensive Center, and clinical research would be actively pursued. Extrinsic residency training programs, coordinated with the nearest Comprehensive Center, would provide additional training for residents in oncology and expand the available patient teaching material. Community support in detection procedures would also be encouraged. Surgeons interested in cancer in the various subspecialties would be on the consultative staff. The number of patients in radiotherapy should be between 75 and 100 a day, and again a population of at least 400,000 people should be served.

* * *

Thus far this discussion has related to large populations in metropolitan areas. The Correlated Oncology Unit is suggested in an attempt to resolve the problem presented by smaller populations and smaller hospitals located at some distance from large population centers. In certain circumstances throughout the country, in sparsely populated regions, some reduction in size and scope of treatment is necessary, but to prevent a concomitant lessening in quality, considerable care must be directed in the planning for these facilities.

In those areas distant from any metropolitan center with a population of at least 100,000 in the immediate medical referral area, the establishment of a Correlated Oncology Unit is recommended. These units could provide optimum cancer care for the patient and still recognize his social and logistical needs. This population would be sufficient to justify a radiotherapist and a medical oncologist who could work together in the correlated unit. The specialists would serve as a focal point in their communities for cancer care. A close relationship with the nearest oncology center, preferably a Comprehensive Center, should be established to provide clinical and radiophysics consultative support. Such a close relationship would expand the scope of the clinical research program of the Comprehensive Oncology Center.

* * *

In the metropolitan setting; the needs of institutions which are not immediately adjacent to an oncology center must be recognized. To ignore these institutions, or to expect passive cooperation involving decisions in which they have not participated, is to invite additional cancer treatment units within the urban area. If a hospital is located some distance from an oncology center, but still within referral distance, and particularly if the hospital has more than 400 beds, it is suggested that an Urban Treatment Unit be formed. The Urban Treatment Unit would be for radiotherapy only, would be administered and staffed by the parent oncology unit, and the center staff would act as a consultative staff to the medical institution for its cancer patients. The patients treated at the Urban Treatment Unit would be, in almost every case, in-patient and palliative; the decision for location of treatment of patients from that institution would rest with the oncology center staff. Although supervoltage should be provided, the limited scope of the equipment and the treatment program would allow a fiscally sound operation with only five or six patients treated daily.

* * *

A full discussion of the cost and fiscal management of these four types of treatment units is beyond the scope of these comments. It is sufficient to state that all of these facilities must be designed with realistic cost considerations, capable of being covered by reasonable patient charges. Prototype centers might be given start-up subsidies, and the most expensive linear accelerators might be provided through philanthropy or government monies, but treatment units should be otherwise self-sufficient. Only in this manner can the general application of these facilities be realized.

Organizational Structure

The organization and governing of these units is of considerable importance to insure a smooth working relationship between the cancer treatment center and the various medical institutions and physicians referring patients to the center.

The bulk of radiation therapy and medical oncology practice is out-patient. Since at least 1200 to 1500 hospital beds would be required to generate 75 radiotherapy patients a day, and since there are very few 1500 bed institutions in the country, there must be coordination with a number of hospitals to justify these treatment centers. Because the purpose of the center is to provide cancer care for a number of institutions within a region, because the nature of the practice is basically out-patient, and because the equipment and staffing needs are unique, it is apparent that such a center need not be within a hospital. Availability of essential hospital-based functions would be assured through affiliated Urban Treatment Units.

If the Comprehensive or Clinical Oncology Center is located outside a university, the governing board should be composed of lay and physician representatives of the medical region expected to refer patients to the center. Funding and administration would be separate from other medical institutions unless located within hospitals of more than 1500 to 2000 beds.

The interrelationships of various treatment facilities which might be found in a region could be coordinated through some form of regional council for cancer. This committee could also serve as a resource if requested by professional groups, medical societies, medical institutions or government agencies in the assessment of further requirements for cancer services. This activity would also be helpful in the blending of cancer services with the general medical development of the region.

Evaluation for the effectiveness of detection, diagnosis, and treatment could be provided through computer-based data retrieval systems. Several of these are now available, capable of input from all the modalities and designed to assess results on a long-term follow-up basis. Constant reassessment would provide suggestions for changes in specific treatment techniques, as well as modifications in the cancer care system.

Conclusion

The cancer patient is entitled to all that modern cancer treatment techniques can provide. The educational and health delivery systems at present are not adequate, in every case, to deliver to the general population that which is available in leading cancer treatment centers. It is not feasible, and it is not the desire of the family physician or the patient to have all cancer patients treated in a limited number of facilities which would have hundreds of patients treated daily. Neither is it desirable that every hospital that can afford a cobalt unit transform itself into a cancer treatment center. The preterminal cancer patients require humane and modern treatment techniques, but this care should not be provided at the expense of the patient who is a candidate for cure of his disease process. The needs of the cancer patient demand creation of an effective system that is based upon sound professional and economic considerations.

Six hundred and fifty thousand people develop cancer in the United States each year. In the most modern centers, where the latest advances in interdisciplinary treatment techniques can be applied, it has been estimated that approximately half of these patients can be cured. Yet, on a national average, only one-third of these 650,000 are being treated successfully. This discrepancy suggests that with adequate personnel, proper organization and planning together with application of already known treatment techniques, it should be possible to improve national cure rates by 15 or 20 percent. Great effort and expenditure in the area of basic cancer research is most certainly required to conquer cancer, and many federal, state and private institutions have been and are being funded for this purpose. With significant improvement in the apparatus for the organization and delivery of the product of this research, tens of thousands of cancer patients will be saved.

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Director, Section of Radiation Therapy
Peninsula Hospital and Medical Center, Burlingame
President, California Radiotherapy Association

SEARCH FOR LYMPH NODE INVOLVEMENT IN CANCER OF THE BREAST

Operative stage I breast cancer is not the same as clinical stage I. If you explore the axilla at the time of operation—after you have mobilized the breast and broken into the axillary space—your accuracy of interpretation of lymph node involvement is approximately three times as great as it is in the clinical examination. As you know in clinical examination, you can't be more than about 70 percent accurate, no matter how good you are. By contrast, you can achieve an error rate of only 10 percent when you examine at the time of operation, looking for the beading of the lymphatics and the consistency (rather than the size) of the node.

—George Crile, Jr., M.D., Cleveland
Extracted from *Audio-Digest Surgery*, Vol. 17, No. 6, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, Ca. 90057

CASE REPORTS

Refer to: McNair JD: Selective coronary angiography: Report of a fatality in a patient with sickle cell hemoglobin. Calif Med 117:71-75, Nov 1972

Selective Coronary Angiography

Report of a Fatality in a Patient With Sickle Cell Hemoglobin

J. Douglas McNair, m.d., *Arcadia*

The purpose of this paper is to show that, in a patient with an unrecognized sickle cell hemoglobin, injection of a highly osmolar material into a coronary artery can produce a fatal arterial occlusion.

Coronary angiography has become a widely accepted procedure since Sones and Shirey[1] described the method of selective injection of the coronary arteries. This investigative examination will, undoubtedly, have wider application with the introduction of the surgical procedures of venous bypass graft, gas endarterectomy, and infarctectomy. Ross and Gorlin[2] reported 3,312 coronary arteriographic procedures in a cooperative study, with 1.9 percent complications. There were three deaths, two resulting because of dissection of the wall of the coronary artery with myocardial infarction, and one from complete heart block and asystole. More recently, Demany et al[3] reported in an editorial that they had performed 15,214 coronary arterial injections in 2,121 patients without a single incidence of ventricular fibrillation, and they concluded that selective coronary arteriography is a safe diagnostic procedure. In none of these large series, however, did a major thrombosis occur during the arteriography.

A 46-year-old Negro man was first seen because of pain in the chest and fatigue, suggestive of coronary insufficiency. He was born in Honduras and had lived in California since 1964. His health had been excellent and there was no history of anemia in the patient or any member of his family.

The patient was well developed and well nourished. Blood pressure was 125/70 mm of mercury and the peripheral pulses were excellent in all extremities and the neck. There was no cardiac enlargement or heart murmurs, but there was a faint third heart sound audible at rest, which increased with isometric exertion and after exercise.

The resting electrocardiogram was within normal limits. The patient was then given a double two-step exercise test of 38 ascents which he completed, although slight substernal tightness developed at 32 ascents. This discomfort lasted for approximately two minutes after completion of the exercise and then disappeared spontaneously. The post-exercise electrocardiogram showed no changes from the resting tracing, but the faint third heart sound at rest had become louder following the exercise. A fourth heart sound was not heard.

The patient was admitted to the hospital for cardiac catheterization where an x-ray film of the chest showed no abnormalities and the cardiac shadow was within normal limits. Hemoglobin was 16 grams and hematocrit 47.6 volumes percent. Erythrocytes were morphologically normal and sedimentation rate was 1 mm per hour. Leukocytes numbered 5,000 per cu mm with a normal differential. Urinalysis was within normal limits. Serum cholesterol was 276 mg and fasting glucose was 88 mg per 100 ml.

Premedications for the catheterization were meperidine hydrochloride (Demerol®) 50 mg, atropine 0.6 mg, and promethiazine hydrochloride (Phenergan®) 25 mg. A 7F Zucker pacing catheter was passed via a right antecubital vein and used to record right sided pressures (Table 1). A 7F left ventricular Cordis catheter was

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Submitted February 18, 1972.

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TABLE 1.—*Catheterization Recordings at Various Positions*

Catheter Position	*Pressure (mm of mercury)*	*Oxygen Saturation %*
Right Ventricle	25/5	75
Pulmonary Artery	22/12	74
Left Ventricle	130/8-10 End Diastolic Pressure 8 mm after pacing	97
Ascending Aorta	134/85	96

Cardiac output at rest, 4.08 liters per min, 2.11 liters per square meter

then passed into the left ventricle via the right femoral artery, using the Seldinger technique. The Zucker catheter was then pulled back to the right atrium and the patient was paced at rates up to 150 per minute with continuous recording of the left ventricular pressure. The patient had no chest discomfort or changes in the electrocardiogram during this procedure.

After hand injecting a few milliliters of Renografin-76* to check catheter position, 40 ml of the Renografin-76 was injected into the left ventricle at 600 pounds pressure for the left ventriculogram. The patient remained asymptomatic and showed no abnormal changes in either the pressures or the electrocardiogram from this injection. The left ventricular catheter was then replaced with a 7F No. 5 Judkins left coronary catheter. The guidewire was removed in the ascending aorta and the catheter was flushed with a heparin solution. With continuous monitoring, the catheter tip was advanced with ease into the left coronary ostium. One milliliter of Renografin-76 was injected to confirm catheter position and the left coronary artery and its branches were briefly outlined on the television monitor screen.

The patient was then positioned for a ciné recording and approximately 2.5 ml of Renografin-76 was introduced into the left coronary artery by hand injection in less than ten seconds after the test injection. Viewing the contrast material on the television monitor during the ciné recording, it was seen to advance only a few centimeters beyond the catheter tip, outlining only the major trunk of the left coronary artery (Figure 1). The pressure monitored through the catheter had shown no change just before or after the injection of the Renografin-76. The catheter was immediately pulled back to the ascending aorta and the pressure, monitored through the catheter, then began to drop on each successive beat down to static levels in about one minute. The patient complained of chest discomfort for the first time; unconsciousness followed, and ventricular fibrillation developed in approximately two to three minutes. Despite all resuscitative measures, including pacing for 1 hour and 45 minutes, the patient could not be resuscitated.

Necropsy*

The heart weight was 350 grams and the pericardium was smooth and glistening. Thickness of the left and right ventricular walls was 16 mm and 2.3 mm, respectively. Multiple sections through the wall of the ventricle showed no gross scarring, softening or discoloration. The endocardium was thin and smooth, and no thrombi were present. The valves of the heart appeared normal. The coronary arteries arose in a normal fashion. However, the right coronary was rather small. It could be opened with the tip of surgical scissors only about half its distance in the atrioventricular groove towards the posterior wall, but it was patent throughout, with only a few small areas of yellow plaque formation in the wall and without any significant narrowing. The main left coronary artery was 12 mm long and was widely patent, with some yellow plaques present. There was a large thrombus beginning at the bifurcation of the main left coronary, extending 2 cm into the left circumflex and 4 cm into the anterior descending artery. It was not adherent to the wall. Both major branches of the left coronary artery were readily followed and there was no significant narrowing at any level. Plaque formation was minimal.

Microscopic examination of the thrombus in the left coronary was consistent with fresh antemortem formation. There were a few well preserved leukocytes enmeshed in fibrin which had undergone some degree of hyaline change. The irregular islands of red cell masses were surrounded by, or related to, the bands of hyalinized fibrin, so that a mosaic structure was seen. Some of the red cells appeared intact, but others blended with adjacent red cells, so that some of them may have been hemolyzed. There also were some areas where irregular, somewhat amorphous streaks of material took a dense he-

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*All dye used in this study was Renografin-76 (meglumine diatrizoate and sodium diatrizoate) with 0.16 mEq of sodium per ml.

*Done by Richard D. Lewis, M.D.

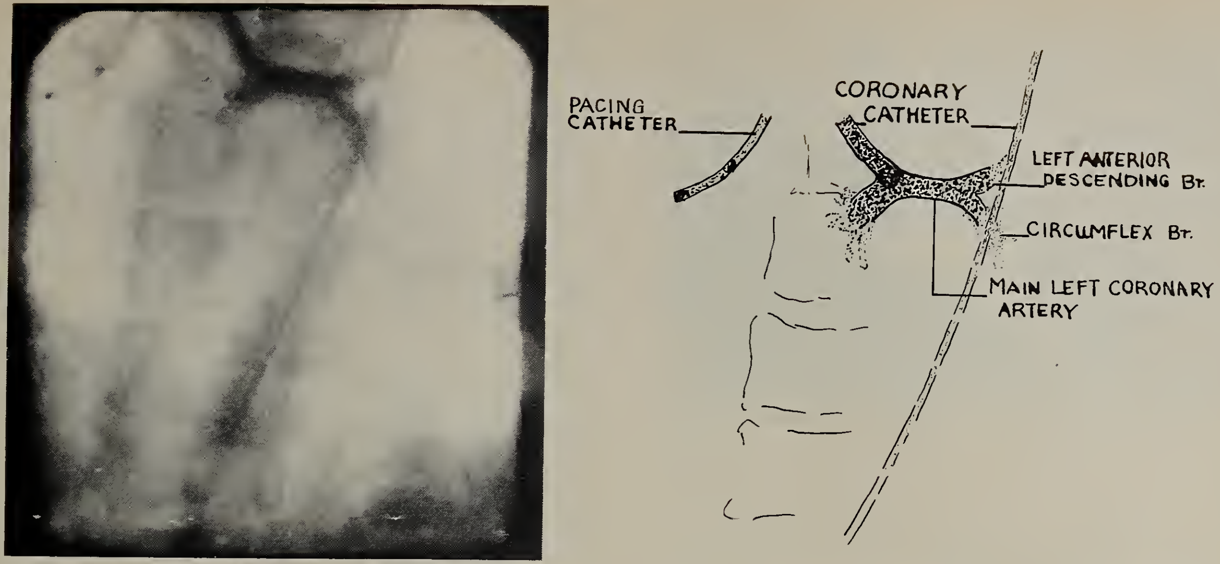

Figure 1.—Retouched enlargement of a frame from the left coronary cineangiogram. The drawing shows the findings in more detail.

matoxylin stain, suggesting release of neucleoprotein from cells. No sickling or foreign material, however, was identified in the thrombus, either under ordinary light or using polarized light.

Multiple sections from various representative parts of the heart were examined and no necrosis or inflammation was identified. There were some fibers which appeared slightly hypertrophied, but no perivascular scarring was seen and small blood vessels appeared to have walls of normal thickness. An occasional larger artery showed minimal sclerosis without narrowing. In one section, a minute focus of dense scarring was seen with slight disruption of muscle fibers, a few of which appeared to be replaced by scar tissue. There was no clear increase in the connective tissue component, and fat was present in only small amounts in the right ventricular wall.

The kidneys were congested and there was some protein precipitate in Bowman's spaces, as well as in many of the tubules. Especially notable in the vessels of the kidney were red cells undergoing sickling (Figure 2). Similar alteration of red cells was seen in other organs. As the tissues were fixed in 10 percent formalin, which causes reduction of hemoglobin and formation of elongated or sickle forms, it cannot be determined if this finding was due to ante mortem or post mortem causes; however, since it occurs only with a sickling disorder, it did confirm the presence of abnormal hemoglobin.

Discussion

Although the cause of sudden thrombosis in this patient cannot be unequivocally established, the most likely would seem to be a combination of circumstances—namely, the presence of a sickling disorder and the rapid introduction of a highly concentrated material with a low pH. Perrillie and Epstein[4] demonstrated experimentally that the sickling phenomenon occurs and can be reversed practically instantaneously in blood from all patients with sickle cell anemia and sickle cell variants when their blood is mixed with hypertonic solutions. Sickling was first noticed at 600 mOsm of the sodium chloride solution. It also was elicited by hypertonic solutions of mannitol or sucrose at 1000-1200 mOsm per kg of body weight, but not by urea. It was felt that the mechanism responsible was cellular dehydration, causing an increased concentration of hemoglobin within the red cell envelope, rather than a specific ionic effect of the high concentration of solution upon the hemoglobin itself.

Cheatham and Brackett[5] performed *in vitro* experiments using a 2.5 percent concentration of sodium and meglumine diatrizoates (Hypaque®) and found that, as the concentration increased, more sickling developed in the blood of patients with SS hemoglobin, and that it was even greater with Conray 60. Rand and Lacombe[6] showed that the injection of a concentrated angiographic agent (Angio-Conray) produces severe hypertonicity and a pronounced drop in hematocrit, and

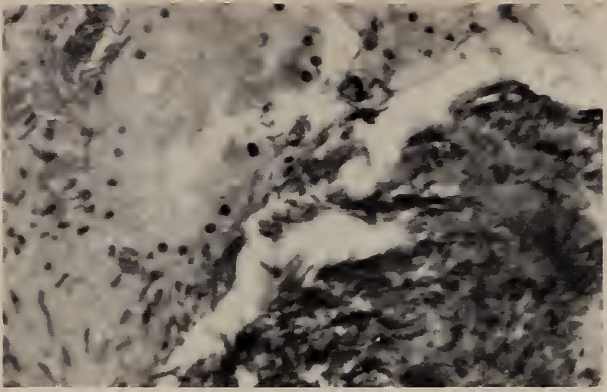

Figure 2.—Microscopic section from the kidney, showing sickling in the vessels (hematoxylin-eosin stain).

that the viscous response of the blood to these agents is primarily related to their hypertonicity rather than to their viscosity. They also found the human red cells to begin to crenate with amounts above 340 mOsm per kg of body weight. A comparison between the hypertonicity of the different angiographic agents was made by Bernstein et al.[7] Using the Fiske osmometer, they found Angio-Conray 80 to be 2264; Renografin-76, 1648; Conray-60, 1382, and Hypaque 50, 1376 mOsm per kg of body weight. These results are somewhat less than those for Angio-Conray 80, estimated by Rand and Lacombe to be between 2400-2800 mOsm per kg, and for Renografin-76, measured by the manufacturer at 6.8 times normal saline solution, or approximately 1900 mOsm per kg.[8]

On the basis of the above mentioned findings of crenation at 340 mOsm per kg and sickling at 600 mOsm per kg, however, most of the angiographic agents would be potentially hazardous at over 10 to 20 percent concentration in patients with sickle cell trait.

A low pH can also cause sickling and increase sickling from other causes. The Renografin used in this study was measured with a pH meter and was found to have a pH of 7.1, which is within the manufacturer's specification of 7.0-7.6. Although slightly alkaline chemically, this pH would be acid in relation to the normal blood pH and might have increased the effect of the hypertonic agent.

Low oxygen tension in the area of the injection also may cause sickling, but this usually takes two to four minutes at body temperature.

There was no evidence of thrombosis or other complication following the left ventriculogram, possibly due to the rapid dilution of the contrast material as it was injected. This injection, however, may have caused an increase in the blood viscosity which then may have become more pronounced in the coronary artery following the test injection at this site.

The cause of the original chest pain in this patient also remains an unanswered question. Despite the onset of a substernal chest tightness associated with an audible third heart sound, typical of angina pectoris,[10] near the end of the double 2-step test, necropsy failed to show significant coronary narrowing.

It would appear, however, that coronary arteriograms should be approached cautiously in all Negroes and that they should be tested for sickling before the study.

Comment

Although a sickling disorder may be a benign condition, it may constitute a potentially serious hazard under certain circumstances, such as high altitude flying, infections, and other stressful conditions. Coronary arteriography should be added to this list.

Summary

A case is described of a 46-year-old Negro man in whom thrombosis developed instantly at the bifurcation of the left main coronary artery after injection of only 1 ml of Renografin-76 into the left coronary ostium. The autopsy findings revealed changes typical of the sickling phenomenon.

It would appear advisable to evaluate all Negroes for the presence of a sickling disorder before performing coronary arteriograms, and if sickling is found this examination should be done cautiously, using all prophylactic approaches possible.

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Refer to: Wyler DJ, Golde DW, Grausz H: Bacterial endocarditis in a patient with a saphenous vein graft A-V fistula receiving dental work. Calif Med 117:75-76, Nov 1972

Bacterial Endocarditis in a Patient with a Saphenous Vein Graft A-V Fistula Receiving Dental Work

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SURGICALLY CREATED arteriovenous (AV) fistulae in dogs have resulted in spontaneous bacterial endocarditis about four to six weeks afterward.[1] This model suggests that patients with AV fistulae receiving hemodialysis could be a high risk group for the occurrence of bacterial endocarditis. Recently reports of bacterial endocarditis associated with the use of subcutaneous AV fistulae in hemodialysis patients have appeared in the literature.[2] We present here another case of bacterial endocarditis associated with the use of a saphenous vein graft AV fistula for hemodialysis.

Report of a Case

The patient, a 37-year-old black man without previous valvular heart disease and with chronic renal failure, entered the hospital in florid congestive heart failure, five months after having begun chronic hemodialysis. He had initially received dialysis three times per week via a Scribner (Teflon-Silastic) AV shunt placed in the right forearm, but when this clotted four months later, a subcutaneous, saphenous vein graft AV fistula was surgically created in the left forearm and the sterile Scribner shunt was removed. At about this time, the patient also began regular visits to his dentist for scaling and filling of carious teeth. Two weeks later, the patient noted sudden onset of fever, chills, weakness and malaise. A false aneurysm in the AV fistula was drained and tetracycline was prescribed, 250 mg a day by mouth. Cultures of specimens from the aneurysm site grew enterococci, while blood and urine cultures at that time were sterile. The fistula healed, and dialysis was continued through this route. Five days before admission the diastolic blood pressure had fallen to 40 mm of mercury. Two days before admission, results of cardiac examination were considered normal.

Past history was of note in that the patient had had a previous anaphylactoid reaction to penicillin.

On admission the patient was acutely ill, with temperature of 38°C (100.4°F), blood pressure of 140/40 and regular pulse at 120 beats a minute. No peripheral stigmata of bacterial endocarditis were present. The patient was in frank biventricular congestive heart failure with a hyperactive precordium and a grade 3/6 systolic ejection murmur at the aortic area radiating into the carotid arteries, as well as a grade 3/6 diastolic murmur heard at the aortic area. Peripheral signs of aortic insufficiency were present. The AV fistula was clinically free of infection.

The patient was given one 80 mg dose of gentamicin intramuscularly and cephalosporin, 2 grams intravenously every eight hours, pending the result of blood cultures, which one day after admission revealed enterococci. The other drugs were discontinued, and vancomycin was given, 1 gram in one dose intravenously. Cultures of two urine specimens, obtained before treatment, were sterile. Despite rapid digitalization, falling diastolic blood pressure and increasing congestive heart failure culminated in cardiac arrest on the third hospital day.

Postmortem examination revealed left ventricular hypertrophy and extensive vegetations on the aortic valve. There was a rent in the noncoronary cusp extending from the base of the cusp to the free margin. The left coronary cusp was also perforated. No inflammatory changes were seen in the genitourinary tract. The left renal artery was 80 percent occluded by a large arteriosclerotic plaque, and the renal parenchyma was that of endstage kidneys with arterial changes consistent with benign nephrosclerosis, but no evidence of pyelonephritis. The AV fistula was not examined histologically.

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Submitted January 21, 1972.

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Discussion

In this case of acute bacterial endocarditis involving a previously normal aortic valve occurring one month after commencing hemodialysis via a subcutaneous AV fistula, it is possible that bacteremia occurred following repeated needle puncture of the fistula during the course of dialysis. However, the type of organism isolated (enterococci) suggests a different source. There was no clinical, bacteriologic or pathologic evidence of urinary tract infection, and the patient had not undergone urological instrumentation before admission. Thus, the genitourinary tract, the most common portal of entry in enterococcal endocarditis, was not the source in this case. On the other hand, the patient underwent dental procedures during the month before the onset of his illness, and resultant bacteremia of enterococci may have been the basis of endocarditis. Although this is an uncommon portal of entry for enterococci, it is important to note that both patients reported by Goodman et al[2] who had endocarditis following dialysis through an AV fistula, had undergone dental procedures just before the onset of acute illness. Moreover, in one of these patients enterococcus was the responsible organism; culture of the other patient's blood grew out S. viridans. In the first patient, the clinical course—including the absence of preexisting valvular disease, acute aortic insufficiency and fulminant congestive failure—was very similar to that in the case we have described.

The pathophysiology of bacterial endocarditis in the presence of an AV fistula without preexisting valvular damage is not well defined, although a number of hypotheses have been entertained.[1,5] One such idea has been that the increase in cardiac output occurring as a consequence of AV shunting results in trauma to the aortic valvular cusps and in an anatomical deformity which increases the susceptibility to growth of organisms on the valve following transient bacteremia. Lillehei et al[1] showed that an AV fistula of greater than 15 mm diameter surgically created in dogs resulted in spontaneous bacterial endocarditis about four to six weeks after creation of the shunt. A clinical correlation comes from the report by Cutler et al,[4] who described a patient with aortic valvular damage and bacterial endocarditis occurring as a result of traumatic creation of an AV fistula.

The susceptibility of the fistula itself to form a nidus of infection for seeding of bacteria is suggested by the work of Rodbard,[5] who noted that hemodynamically the flow from a high into a low pressure sink as well as alteration in laminar flow through this area may play a role in infection at this site. Possibly certain altered host defenses found in renal failure[6] contribute to the pathogenesis of endocarditis in this setting.

While the relationship between AV fistulae and bacterial endocarditis has not been definitely demonstrated in humans, from the increasing numbers of cases reported to date, it seems advisable that patients with such fistulae should receive prophylactic antibiotics while undergoing dental procedures. The choice of drugs should be directed against both vividans and enterococcus groups of Streptococci. Thus a combined penicillin and streptomycin regimen, or vancomycin in patients with hypersensitivity to these agents, should be recommended. In light of the underlying renal failure, dosage should be appropriately adjusted. In the case of vancomycin, the fact that this antibiotic is non-hemodialyzable must be taken into consideration.

Summary

Case reports of septicemia, septic pulmonary embolism and bacterial endocarditis have been associated with the use of subcutaneous arteriovenous (AV) fistulae in hemodialysis patients. In the case, here presented, of bacterial endocarditis occurring in a patient undergoing chronic hemodialysis with a subcutaneous AV fistula, the patient was undergoing dental procedures in the weeks before the onset of infection. This case and two other previously reported cases suggest that patients with AV fistulae undergoing dental procedures should receive prophylactic antibiotics whose spectrum includes coverage against enterococci.

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LETTERS *to the Editor*

One Rx at a Time

To the Editor: In recent years there has developed a practice of prescription writing that has a potential for danger. An increased number of physicians have begun to write two or more prescriptions on one prescription blank.

Many pharmacists have complained of this practice to their professional associations and these are some of the reasons they feel it will promote increased error. By law the pharmacist is required to place on each prescription the following information; the Rx number, date filled, the initials of the pharmacist, the quantity dispensed, and a large C must be stamped in the lower right hand corner if a control drug is written. Refills must have the date refilled, the initials of the pharmacist, and the quantity dispensed. By common practice, the pharmacist adds the following information: the brand or manufacturer if a generic drug is written for, the price and several other items if a Medi-Cal or other third party payment plan is indicated. *The crowding of all this information into a relatively small space leads inevitably to errors.*

Errors that can occur are: the labeling of one drug with the directions of another drug which appears on the same blank, the quantity of one drug being dispensed for the other drug, on refills, the patient may order one drug and the other drug is dispensed. These are some of the problems we are concerned about.

We urge all physicians to write just one prescription per blank. Thank you.

MARTIN LEVINE
Professional Liaison Committee
California Employee Pharmacist Association
Panorama City

The Adequate Coronary Arteriogram

To the Editor: The widespread demand for coronary arteriography presupposes that the study will reveal the status of the coronary vessels in sufficient detail to guide appropriate medical or surgical therapy. To ensure this happy outcome it is necessary, however, to have clearly in mind what constitutes an adequate coronary arteriogram and to take appropriate measures to see that the result lives up to the expectation. With the abandonment of all indirect methods it may be taken for granted that it is necessary to insert an appropriate catheter into each coronary artery, to inject a quantity of opaque material which is neither so small as to be useless, nor so large as to be dangerous, and to record the resulting image in an acceptable fashion. To accomplish the catheter insertion and the injection requires skill and experience above the ordinary and, not infrequently, a bulldog tenacity. The standard methods are those of Sones[1] and Judkins.[2] Each has its adherents and each is capable of producing excellent coronary artery opacification. Strangely enough, it is in the third and simplest requirement, the recording of the image, that most of the uncertainty and controversy lies and it is this aspect of the examination which is most often inadequate.

It is an accepted principle in radiology as in criminology that two views at right angles constitute a desirable minimum for identification. If the coronary arteries were simple, immobile structures like long bones, any two views at right angles would probably suffice. The coronary arterial patterns are, however, extremely complex with segments and/or branches proceeding in virtually all directions, changing direction frequently, and performing virtually ceaseless acrobatics throughout the filming. Add to this the fact that it is necessary to see every segment of every artery and every branch 1 mm or more in diameter as a bare minimum, and it becomes evident that two views at right angles cannot possibly constitute an adequate coronary arteriogram. Neither can it be adequately recorded without the high frequency exposures (30 to 60 frames/sec) available with motion picture cameras. Finally, it is necessary that in the viewed image vessels appear at least twice their natural size and preferably more. Otherwise there is no possibility of evaluating the degree of narrowing of a vessel of one millimeter diameter.

Ideally, one would like to see the vessels from all angles but limitations of volume of opaque medium and radiation exposure make this impossible. In our institution we settle for high and low left oblique views and one right oblique view of the right coronary artery, and high and low left oblique views with one postero-anterior and one right oblique view of the left coronary artery. These are all recorded on 35 mm cine film. Sones and Judkins, the acknowledged leaders in the field, record at least three or four views of each coronary artery. It would be rash indeed for the rest of us to suppose that we can get by with less. Furthermore, it is necessary that each view be adequately injected, properly panned, and properly recorded.

There is no doubt that coronary arteriography can be, and frequently is, a tedious and exacting task. Nevertheless, excellent arteriograms are turned out daily in the better laboratories with virtually 100% success. These results are not achieved without proper training, skill, knowledge and determination. It ill-behooves one who is lacking in any of these areas to undertake the task.

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An Answer to a Call for Help

To the Editor: In response to Dr. Kal's question, "Why this apparent reluctance to ask for psychiatric consultations?" [A call for help (Letter to Editor). Calif Med 117:82, Sep 1972], three points: Firstly, many physicians are admittedly still reluctant to acknowledge psychiatry as "real medicine" and therefore hesitate to make appropriate referrals. Secondly, on the other side of the fence, some psychiatrists who are competent therapists are less skilled as consultants and may have alienated some of their colleagues. But thirdly, and most importantly, many psychiatric patients in Dr. Kal's experience were apparently referred to public health nurses who in turn asked for consultation. Properly qualified public health nurses in cooperation with a consulting psychiatrist are an excellent treatment source and I would encourage expansion of this arrangement.

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Isoniazid Chemoprophylaxis

To the Editor: I received a letter from Dr. J. Yerushalmy, Professor of Biostatistics at the University of California at Berkeley, with regard to our article on Isoniazid Chemoprophylaxis (INH) in the April issue of California Medicine.[1] He reminds us that in the Public Health Service trials of INH chemoprophylaxis in household contacts and mental institutions the mortality rate was actually higher in the INH group than in the controls for non-tuberculosis deaths.[2] This point was discussed by Mrs. Shirley Ferebee who pointed out that by chance the INH group was sicker to begin with and that careful case review provided no basis for implicating INH in any of the deaths.[3] I have not found any more recent information on this subject, but I agree with Dr.

Yerushalmy that the question is still not resolved and that INH may have harmful effects. For this reason we tried to emphasize, first, the known undesirable effects of INH and, second, the relative risk of developing tuberculosis which in some groups is relatively low anyway (see Table I of our article[1]). We did include the recommendations of the Public Health Service for groups requiring chemoprophylaxis as part of our conclusion, but implied that the decision should be made on an individual basis and that the important thing was to be aware of the increased risk of tuberculosis in these groups whether INH was given as chemoprophylaxis or not. As Dr. Yerushalmy pointed out in 1967, the United States Public Health Service data could mean that prolonged use of INH leads to an increased mortality.[4] As in 1967, no data is available to refute this point with statistical certainty, although in the other USPHS trials this difference in non-tuberculosis deaths in the INH and control groups was not evident.

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Health Insurance Payments

To the Editor: This letter is in reference to the article on physicians, unions and guilds appearing in the September, 1972 issue. At least one reason for the development of a physician's union or guild, from the standpoint of the private practitioner, has been the failure of organized medicine of effectively dealing with the abuses by insurance companies, of doctors and patients. In brief, there is a radical asymmetry in the obligations of the patient and the insurance company. The purchaser of an insurance contract is under an obligation to make timely payments for insurance within a grace period, in order to maintain his protection under the contract. However the insurance company is under no obligation to make timely payment under the contract, and there is no penalty for procrastination, in the event a claim is submitted.

Since it is advantageous to the insurance company to delay payment as long as possible, many techniques have been developed to insure that payment is slow and partial. These include real or feigned loss of claims, requests for unnecessary additional information (which may be "lost"), alterations of numbers, partial payment, and utilization of peer review, as a delaying action. Even when peer review has been completed and further payment is authorized, further delays or refusal to make payment may still ensue, requiring court action. These delays are difficult for the doctor to combat since the insurance contract is with the patient and patients usually aren't familiar with such stalling tactics, or due to their medical problems aren't capable of vigorously pursuing their own interests.

The net result is that physicians are spending more and more of their time battling insurance companies for themselves and their patients, at increasing expense, whereas insurance companies profit from the money they don't pay out, despite what may be proven to be their obligation.

One avenue of relief would be legislative, namely a requirement that insurance companies be obligated to pay all claims within a grace period, for example, 30 days. After an additional 30 days, punitive interest charges should be assessed. The idea is not to punish the insurance companies of course, but merely to insure that they behave in an efficient and responsive manner. Physicians have peer review, but there is no peer review for insurance companies, nor even a standard by which to judge if they are discharging their obligations fairly and efficiently.

I have previously written letters to officers and committees of the California Medical Association, Santa Clara County Medical Society, and the California State Attorney General and Insurance Commissioner, without effective response or useful comment. Perhaps it will take a physician's union to achieve equity. The union weapon need not be a "strike" against patients, but against the private and public bureaucracy that is unresponsive to problems.

ROBERT S. LICHTENSTEIN, M.D.
Mountain View

Refer to: Ford JH: Mass-produced, assembly-line abortion—A prime example of unethical, unscientific medicine (Controversial Ethical Issues). Calif Med 117:80-84, Nov 1972

Controversial Ethical Issues

Mass-Produced, Assembly-Line Abortion

A Prime Example of Unethical, Unscientific Medicine

James H. Ford, m.d., *Lynwood*

■ *The incidence of psychologic sequelae associated with abortion cannot be established scientifically, and so continues to be disputed. Since there are no truly scientific criteria on which to make a prediction as to the psychologic outcome, it seems only proper that elective abortion be labeled "experimental," rather than "therapeutic."*

This uncertainty as to therapeutic benefit is compounded by the fact that adequate studies and information about physical sequelae are also lacking. Furthermore, preliminary statistics from the Population Council indicate that the morbidity rate of abortion performed even under proper medical auspices is unacceptably high.

Viewed in this light and in relation to our own ethical code, the current practice of performing innumerable, mechanized, elective abortions can only be considered unethical. If it is argued that abortion can be ethically validated merely by surrounding it with the same controls used in other experimental procedures, then the medical profession should insist on such controls forthwith.

> *"A physician should practice a method of healing founded on a scientific basis; and he should not voluntarily associate with anyone who violates this principle."*
>
> —Section 3: AMA Principles of Medical Ethics

"We must re-affirm . . . that any therapy or manner of management which has potential risk for the patient must be validated by means of the experimental method as well as by well-designed and controlled clinical trials before use. It must be kept in mind that a number of treatments, generally accepted in wide use today have not been so validated."[1]

This quotation is taken from a recent discussion on the therapy of myocardial infarction by two internists; but as a statement of sound principle, it has a considerably greater applicability to the practice of electively induced abortion, which has become so mechanized and routinized and generalized as a "therapy" for pregnancy that we now have in California and New York what is coming to be known as an "abortion explosion."

It is axiomatic that induced abortion, like all

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surgical procedures, has a certain minimum of irreducible early and late complications, both physical and psychological, even under the most ideal medical auspices. This procedure has a considerable morbidity, and not an insignificant mortality; so, generally speaking, it would seem to be a very poor substitute either for pregnancy prevention or even for term delivery. Even Dr. Keith Russell, who has been most enthusiastic as a leader in the movement toward more liberal abortion laws, apparently realizes this.[2,16]

Tietze and Lewit[3] (among a number of other pro-abortion enthusiasts) have admitted that, although large numbers of abortions have been performed, information about the effects of the procedure has been scarce and that little is known, for example, about early morbidity or later sequelae of abortions performed under medical auspices. Tietze[4] points to a Joint Program for the Study of Abortion, sponsored by the Population Council, which indicates that the risk in the first trimester of pregnancy is 1 in 20 for minor complications and 1 in 200 for major complications. This morbidity rate was higher after the first trimester. (It is important to note that the people who gather and report such statistics are, obviously, strongly pro-abortion. Consequently, they would more likely tend to understate the degree and number of complications, rather than the converse.)

What this means, then, is that among the 400,000 "legal" abortions reportedly done in 1971, there was a minimum of 2,000 women who suffered major complications in the form of hemorrhage, pelvic infection and uterine perforation; and there was also a minimum of 20,000 women who suffered lesser complications.

Noting the rather significant morbidity (especially after the first trimester) resulting from what has become, essentially, an elective procedure, Tietze and Lewit[3] suggest that the lesson to be learned is that "quick diagnosis of early pregnancy should be made available to all women"; their main message being, therefore, that abortion should be done as early as possible to avoid the complications. But these authors apparently failed to note that this policy may not be a cure-all in that the earlier and quicker the diagnosis, the greater the possibility of its being incorrect.

They demonstrate this point inadvertently in relating the case of "an 18-year-old 'primigravida' who committed suicide three days after a suction procedure because she felt guilty about 'killing her baby.' This death was doubly tragic because the patient committed suicide before the pathology report arrived and she could be told that she had not been pregnant." (In passing, I cannot help observing, quite pointedly, that this is one kind of harmful, diagnostic and judgmental error that certainly does not and cannot occur when the physician's primary goal in managing a pregnancy is term delivery, rather than abortion.)

And in the context of the specific case cited, one is moved to suggest the desirability of investigating the possibility that there might be more of such panicky young girls who, inadvertently (because some eager, pro-abortion physician made the suggested, "early"—but incorrect—diagnosis of pregnancy), had a completely unnecessary "abortion,"—with its attendant risk of serious morbidity, guilt and mental anguish. For example, take the study by Aren and Amark[5] in 1950-52 of 244 legal abortion applicants in Stockholm. They found that seven women (3 percent of the group) to their surprise were not pregnant, and that their worries and the extensive pre-abortion inquiry were quite unnecessary. (Relative to this, it is possible that such an extensive pre-abortion inquiry might be one means to reduce some of the other abortion abuses and excesses in this country; just as it has in Sweden.)

If one is able to use various Public Health Department figures from New York and California as any sort of an indicator, more than 95 percent of the 400,000 legal abortions performed in the United States in 1971 were done for mental health reasons or "psychiatric indications." According to such official reports then, the medical criteria justifying legal abortion have become, for the most part, psychiatric.

But Dr. Alan Stone of Harvard[6] cites the Group for Advancement of Psychiatry report[7] and Sloane[8] to the effect that there are no consistent or valid criteria on which to base the "psychiatric indications" for abortion. And alluding to the period, a few years ago, when psychiatrists had a monopoly on the decision-making process in abortion, he had this to say: "As a profession we made decisions for which we were totally without expertise. . . . The lesson seems clear: if we could be wrong when we decided what was best for pregnant women, how wrong might we be in other situations . . ." Relative to this, Stone remarked, quite pointedly, that it is no surprise that critics have begun to question the role of psychiatry in modern life, when they see the psychiatrist giving advice as if he knows what is best; while in fact, he does not.

In a similar vein, Whittington,[9] after much soul-searching, concluded that psychiatry has once again been caught up in the "delusion" that it is indeed a scientific discipline capable of predicting human behavior in the context of a variety of external events. "The reality is, however, that we do not have the capacity to predict, with any degree of certainty, which women will experience major psychiatric illness as a result of unwanted pregnancy."

(It should be noted, in passing, that an overwhelming majority of the physicians being quoted here are strongly pro-abortion.)

And way back in 1965, Rosenberg and Silver,[10] after a poll of 100 random psychiatrists in northern California, found "a marked lack of consistency and uniformity in the attitudes and practices of the psychiatrists who are called upon to give opinions concerning psychiatric indications for abortion." And further: "The extreme range of opinion represented among the psychiatrists is a far cry from the scientific objectivity that one hopes would apply to determinations affecting the life and health of patients."

Referring to an observation by Bolter,[11] Rosenberg and Silver noted that the psychiatrist "may be manipulated into distortion and exaggeration of the patient's disturbance," with the consequence that the clinical situation comes to approximate the requirements of the law in order to obtain the abortion desired by the patient or her physician; and in some instances, "iatrogenic pressures intensify symptoms so that discontent becomes illness." They also pointed out that the area of abortion is one of the few in psychiatric practice in which psychiatrists readily take a role in dealing with a symptom and the management of a symptom as a primary maneuver. "This is highly contrary to the general current in psychiatric principles. . . ."[10]

To recapitulate: A review of some of the most oft-quoted, and presumably quite authoritative, psychiatric literature on the subject of abortion[5-36] appears to substantiate the posited fact that most honest and knowledgeable psychiatrists have now come to admit that they find themselves out of their depth in this matter of the psychiatrically-indicated abortion decision. But the disavowal by psychiatrists of this decision has left it, by default, to the non-psychiatrist attending physician or to the ambivalent, emotionally unstable, pregnant woman herself. It is perhaps relevant at this point to remind ourselves of a wise maxim left to us (I cannot recall who the sage was) with regard to resolving complex issues or making difficult decisions. As best I can recall, it went, roughly, something like this: "Where experts cannot agree, fools may choose."

In spite of these considerations, liberal abortion proponents, generally, continue to suggest (by their persistent use of the term *therapeutic*) that abortion, even when done mechanistically on a massive scale for social reasons, is automatically beneficial for any and all women who might request it. The implication of that term *(therapeutic)* is that the abortion does measurably more good than harm in the large majority of patients, with the further implication that this beneficial preponderance tends to be permanent —that is, that both the early, and the late, results are good. I think that the tenuous data and contradictory opinions and conclusions found throughout the psychiatric literature are compelling evidence that the case is not yet proved.

Of course, most of the psychiatrists quoted here, being very strongly pro-abortion, have been chiefly concerned that no psychiatrist ever disapprove any abortion, or pretend to any expertise in predicting an unfavorable outcome for any woman who herself might choose abortion over term delivery. But let me emphasize this: What they fail to see, on the basis of the very same evidence, is that the converse is equally true. No psychiatrists (or anyone else, for that matter) can pretend to any expertise in predicting a *therapeutic* outcome for abortion.

Dr. Edmund Overstreet[12] has been one of the leading proponents of easy abortion over the years in California. But even while referring to induced abortion as "therapeutic," he admits that it is no longer a "truly medical" matter, but rather a "sociologic" one, "since physicians increasingly use it simply to solve the problem of unwanted pregnancy . . ." This incongruous use of the euphemistic term *therapeutic* in discussing sociologic abortion in order to hide its social-engineering implications is not unique to Dr. Overstreet, but is quite common among easy-abortion advocates.

But Dr. Overstreet[12] himself is apparently well enough aware of the glaring contradictions in the available studies and of the dearth of any scientific data and criteria that might conclusively establish the therapeutic value of what has now become, in practice, sociologic abortion on a massive scale. He admits that "more studies . . . are needed, using the meticulous methodology [of Meyerowitz et al[13]] to reassure physicians that in performing huge numbers of legal abortions they are doing more good for society than simply satisfying a sociologic whim or coping with population pressure."

Apparently, then, we do not yet fully comprehend the ultimate psychological implications for the individual and the adverse implications for society—especially when elective abortion is performed on a massive scale. An extensive review of the literature[5-36] on the psychiatric aspect of abortion, as was indicated previously, has revealed very little correlation or cross-validation of findings or conclusions that might place the abortion decision on a sound, scientific basis.

On the other hand, as Bolter[11] reminds us, there are certain fundamental biological facts which influence the psyche of our patients. "The ability of mothers to accept infants after they are born is underrated and underestimated. We also are much too quick to accept trite statements and poorly controlled studies about the influence of so-called sick mothers upon their children."

He further points out that child-bearing is a basic biologic and psychological function of a woman: and that, if this function is interfered with too much, the climax of the emotional repercussions is often not reached until the menopause, when she realizes that she can no longer reproduce her own kind. As he puts it: "This is not just textbook theory, as all who practice psychiatry well know."

Then Bolter asks, quite pertinently: "In the face of all this evidence for unconscious influences in women's attitudes toward pregnancy, how can we accept a conscious statement from a woman to the effect that she does not want a certain pregnancy? If we have learned anything in psychiatry, we have learned to respect the unconscious far more than the conscious and we have learned not to take statements at face value."

But according to Dr. Seymour Halleck,[14] many psychiatrists have given up making any effort toward objectivity, or a scientific orientation, or at finding the hard truth in this matter. Having already accepted it as fact that "psychiatric neutrality is a myth," they have eagerly embraced the role of social visionary or political activist in the direction of their own personal philosophy.

We have already made an indirect reference to Sloane's statement[8] that "there are no clear-cut psychiatric indications for therapeutic abortion . . . 'Humanitarian' reasons frequently determine the decision although they may masquerade under psychiatric labels." But Halleck[14] is considerably more blunt. He says that the physician who makes a recommendation for abortion on the basis of an alleged psychiatric illness may be well-meaning, but he is "usually lying." As he puts it: "To salve their professional consciences. they [psychiatrists] subtly teach the patient to be as sick as possible and say the right words—'I'll kill myself if I'm forced to have this baby' before they write the psychiatric excuse."

Relative to this refreshing candor displayed by Dr. Halleck, I believe that psychiatrists, as a group, have much to gain in renewing the confidence of the rest of the medical profession, and of the public at large, by continuing to help us clear up the widespread confusion that has been caused by the contradictory statements and unsubstantiated opinions that have been put forth by so many of their own psychiatric colleagues on the subject of abortion, in the recent past. Relevant to this, Freud said: "To be completely honest with oneself is the best effort a human being can make."

All of which is only intended, finally, to point up the validity of the statement by Dr. Samuel Nigro in a letter to JAMA (2-21-72): "The study of Ford et al,[15] underscores the unethical nature of abortion insofar as it is a procedure not founded on a scientific basis as required by Section 3 of the [AMA] Principles of Medical Ethics. Abortion cannot be called 'therapeutic' . . . It can only be called 'experimental,' and thus it should not be performed except as a part of a systematic program, competently designed, under accepted standards of scientific data, to produce data which are scientifically valid and significant. Abortion is still an experimental procedure, inadequately studied, with no demonstrable therapeutic value, with no clear cut or unequivocal indications, and with unknown future complications."

In the same vein, Nicholas Eastman and Keith Russell tell the pregnant woman in *Expectant Motherhood*[16] (and I see no reason that this should not apply with equal validity to physicians): "Accustomed though we may be in this age of machinery, science and 'free thought' to disregard natural phenomena, pregnancy is one process of nature with which it is best not to tamper." (Ecologically-minded naturalists, please take note.)

In a similar but more sophisticated vein, Meyerowitz et al[12] concluded after their recent meticulous study of the subject: "It is to be hoped that all requests to interrupt a pregnancy will be evaluated thoughtfully . . ."

Notwithstanding any disagreements we physicians may have as to the rights of the fetus in this matter, we surely can agree that we have a minimum professional responsibility, as part of our traditional ethic, to protect the public and to be reasonably certain, on the basis of scientifically sound information, that any induced abortion recommended by a physician will not be detrimental to the ultimate health and welfare of any women—unless adequate warning of the risks and uncertainties has been given beforehand.

Not long ago, the AMA Judicial Council called on all physicians to unite in condemning commercialization of abortion, and abortion mills. In a similar spirit, I now call on all ethical physicians to unite in condemning the practice of routine, mechanized, massive abortion, now in general use in New York and California, among other states—at least until further reliable studies can put its therapeutic value on a sound scientific basis.

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Special Article

A Family Practice Survey in Ventura County

JAMES W. VILLAVECES, M.D., AND WAYNE H. WELCHER, M.D.,*
Ventura, AND GERALD R. EVANS, PH.D., *Los Angeles*

■ *Seventy-five percent of family practitioners in Ventura County, California, responded to a seven-page mailed questionnaire. One third of the practitioners do no obstetrics. The physicians counsel seven patients to every delivery performed and to every surgical procedure performed. Family practice consists of medicine and pediatrics, rather than surgery, obstetrics and psychiatry. Family practitioners use referrals to community health care services in a limited fashion. Lack of information about availability of community resources may be the reason.*

THIRTY-EIGHT YEARS AGO more than four out of every five physicians in private practice declared themselves to be general practitioners.[1] By 1968 this proportion had dropped to 15 percent, with increased specialization. Then in 1957, the realization that someone was needed to assume responsibility for the patient's continuing health needs led to a re-evaluation. A committee was appointed on Preparation for Family Practice.[2] This led to the establishment of new residency programs, and eventually to the formation of a new specialty board in Family Practice.

To better understand the role of the family practitioner, a survey was conducted in Ventura County.

Method

The questionnaire was either mailed or personally delivered. With the questionnaire a cover letter from the Director of Medical Education was enclosed expressing the purpose as well as inviting the recipient's considered cooperation. Initial non-respondents were contacted with a second questionnaire and cover letter. There was a total of 71 respondents out of 96 for a return rate of 75 percent, this proportion agreeing favorably with other surveys of this type.[3,4,5] For many of the questions these categories were used: Medical, Surgical, Pediatric, Obstetrics-Gynecological and Psychiatric.

Results

Forty-three percent of the respondents fell in the age group 36 to 45. The second largest group was 46 to 55. The respondents were all male family practitioners with a median age of 41. Approximately one half had completed a general or family practice residency. The average number of years in practice for the respondents was 13.5. The largest number of practitioners (26 percent) had been in practice for six to ten years. A large group (19 percent) have been in practice for over 25 years.

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Reprint requests to: J. W. Villaveces, M.D., Medical Education Department, Ventura County Hospital, 3291 Loma Vista Road, Ventura, Ca. 93003.

Type of Patient Seen in the Office: (Medical, Surgical, Pediatric, Obstetrics-Gynecological, and Psychiatric)

It was clear from the survey that medical patients were the most numerous. A majority of practitioners see 11 or more medical patients in the office each day. Pediatric patients also make up a large category. A few obstetrics-gynecological and surgical patients are seen each day by a small number of physicians. Almost no physicians said they saw psychiatric patients in their offices.

Type of Patient Seen by the Family Practitioner in the Hospital: (Medical, Surgical, Pediatric, Obstetric-Gynecological and Psychiatric).

Again, medical patients were most frequently seen by the largest number of physicians. Almost all physicians see an average of one or more such patients each day. Surgical patients are the next most frequently seen. Most practitioners see at least one surgical patient each day in the hospital, and 20 said they see at least two per day. Only nine physicians said they see three or more pediatric or obstetric-gynecological patients a day. Practically no part of the family practitioner's hospital day is taken up with psychiatric work.

Type of Patient Seen with Chronic Condition in the Office: The chronically ill do not occupy most of the physician's work day. When he devotes time to chronic care treatment, it will most likely be the diseases of the aged with deterioration of heart, lungs and joints. While few practitioners see acute psychiatric conditions, a significant case load of chronic psychiatric cases is part of their practice.

Diagnostic Procedures Used by Family Practitioners: Most of the family practitioners surveyed used one or more formal diagnostic procedures. The diagnostic techniques most used correlate with the types of problems the practitioners see in the office and at the hospital. X-ray services are needed. The most common types of x-ray procedures are listed in Table 1. If a family practitioner makes use of office x-ray techniques, he is most likely to be concerned with extremities. Chest films are next most common. It is unlikely that a general practitioner will be involved in upper gastrointestinal series, lower gastrointestinal series, intravenous pyelogram, gallbladder series or other x-ray procedures.

TABLE 1.—*Number of Practitioners Using Six Office X-Ray Procedures*

Type of X-Ray Procedure	*Number of Physicians*
Long Bones and Joints	35
Chest	26
Small bones (hands, feet)	19
Skull	17
Flat plate of abdomen	16
Back	14

Other Diagnostic Procedures: Several diagnostic techniques in addition to x-ray procedures are commonly done by family practitioners. The three most commonly stated—urinalysis, electrocardiograms and sigmoidoscopy—are done by the majority of physicians responding. Complete blood cell count, urine Gram stain and tonometry are the next most common techniques mentioned, typically used by about one out of three general practitioners. Other procedures, such as spinal taps, sputum culture and pulmonary function tests are used infrequently.

Treatment Procedures Used by Family Practitioners: One of the major purposes of this survey was to determine the extent to which family practitioners are involved in various types of treatment procedures. The topics chosen for study were surgery, surgical assists, deliveries and counseling of patients.

Surgery Performed by the Family Practitioners:

While some family practitioners engage in little or no surgery they are a minority. About half of the survey sample performed a fairly wide range of procedures, although clearly the number of cases is small considering the schedule of surgery maintained by a specialist in this field. The most frequent surgical procedures performed by family practitioners are presented in Table 2. If a family practitioner is involved in surgery it most likely will be a biopsy, tonsillectomy and adenoidectomy, or fracture setting. About half of the practitioners perform these procedures, or the next most common, dilatation and curettage, hernia or appendectomy, at least once a month.

Surgery in Which the Family Practitioner Assists:

Many family practitioners typically assist surgeons. The physician either assists because it is his practice to do no surgery or because he does

TABLE 2.—*Number of Procedures per Physician per Month in Ten Main Categories*

Type of Procedure	*0*	*1*	*2*	*3 or more*
Biopsy	5	15	20	24
Tonsils and Adenoids	17	12	16	20
Fracture Setting	14	15	20	13
Dilatation and Curettage	10	34	15	4
Hernia	25	24	10	4
Appendectomy	23	30	7	1
Hysterectomy	36	19	6	1
Hemorrhoids	23	35	3	0
Cesarean section	34	23	1	1
Cholecystectomy	37	25	1	0

only the less complicated procedures on his own and calls in a specialist for cases in which his own experience is more limited. About once a month the practitioner is likely to assist in operations for hysterectomy, hernia, appendectomy or gallbladder. Family physicians are less involved in other types of major operations such as abdominal, chest or vascular procedures.

Deliveries Performed by the Family Practitioner: Almost one-third of the family practitioners surveyed report they do no deliveries at all. A smaller group do one or two deliveries a month. Some physicians devote considerable time to obstetrics; over half the survey respondents perform one delivery a week or more. Further study of data on physicians not performing deliveries and those actively engaged in obstetrics indicates that the practitioner who performs five deliveries or more is younger and more likely to have had a general practice residency.

Counseling Performed by the Family Practitioner: In addition to medical consultation, surgical procedures and deliveries, most family practitioners are called on to give some counseling on an amazing variety of topics. These may include, in a typical week, two or more psychosomatic conditions, marital problems, individual adjustment problems and sexual difficulties. These data agree with reports by other investigators.[6,7] Other conditions in which counsel is given are senility and discipline problems, although the practitioner tends to avoid getting involved in alcoholism and drug addiction problems.[8,9,10] The number of family practice physicians who do no counseling in addition to their strictly medical duties is small.

It is significant that in an average month, the family practitioner gives counsel for psychological problems to seven times as many patients as he delivers, and also seven times as many as his number of surgical procedures. From their answers it appears that family practitioners do not consider their counseling to be the practice of "psychiatry."

Referral Patterns of Family Practitioners: While diagnostic and treatment patterns are important to an understanding of the family practitioner and his practice, his patterns of referral are equally interesting. The physician can refer his patient to another physician, or to a community health agency. This latter type of referral has become one of increasing importance in the new family practice specialty.[11,12]

Practitioners referred from one to four patients a month to specialists. The patients tended to be either medical or surgical and the numbers partially relate to the number of patients seen in these categories. Pediatric patients were referred, on the average, least of all.

Practitioners were asked to choose reasons for referral of patients. "Not enough time" was marked by 18, while 62 marked "special diagnostic skill needed" and 65 marked "special treatment skill needed."

The most frequent patient referrals to agencies by family practitioners are to mental health, to a social worker, to a physical therapist and to Alcoholics Anonymous. Over half of the practitioners indicated they used these community health resources. In decreasing order of referrals were: minister or priest, speech therapist, occupational therapist, maternal and child health, remedial reading, cerebral palsy, legal aid, visiting nurses, and Crippled Children. When practitioners were asked why they might have difficulty in referring patients to community health agencies, they mentioned that they had little familiarity with the community's referral facilities. Others had received poor advice regarding availability of services and had trouble placing patients.

Specialization and Preference Within Family Practice: The respondents were asked to rank their interests in the five practice categories of medicine, surgery, pediatrics, obstetrics-gynecology and psychiatry. The respondents marked medicine as their special interest in 45 percent of the cases (32 physicians). Forty-one percent ranked surgery first. Only 13 percent ranked obstetrics-gynecology at the top, and 7 percent ranked pediatrics first. Psychiatry drew the smallest interest response with six percent.

In another question the respondents were asked to indicate their interest in doing more or less of the five categories mentioned above. For example, "If I had a choice I would prefer to do more (or less) surgery." An "interest in community activities" category was included. Forty-one percent indicated a wish to do less surgery. Forty-two percent of the respondents (31 physicians) preferred to do less psychiatry and only 14 percent would like to do more. Forty-two percent would choose to do more community activities, while 14 percent would like to do less.

In order to determine if there were some patterns in the monthly activities reported by the survey sample, each item was summarized on a three or four point scale from "none" to "low involvement," through "moderate," to "high involvement" in the particular topic. The relationships among these scores with one another were then statistically determined. A correlation coefficient was used. Six major areas of medical activity were thus identified: Area 1, pediatrics; Area 2, obstetrics-gynecology; Area 3, internal medicine; Area 4, surgery; Area 5, counseling; and Area 6, chronic care. The correlation coefficients for one set of major activity, Areas 1, 2 and 4, were highly homogeneous. This type of practitioner tends to concern himself mostly with pediatrics, obstetrics-gynecology and surgery, but in a context of a practice which includes concern for internal medicine and counseling. These practitioners are relatively less involved in the care of chronic diseases. In fact, most will not have even one patient in a nursing home. These practitioners tend to be somewhat younger. The correlations between major activity Areas 3, 5 and 6 indicate the presence of another interest pattern. These practitioners tend to do internal medicine, and see counseling and chronic care patients. These physicians have few distinguishing characteristics, other than their involvement in these areas and the fact that they are somewhat older.

Discussion

This survey comprises one of the few questionnaire investigations of what family practice is really like. In 1956 Peterson, Andrews, Spain and Greenberg documented one of the most complete studies of this type ever done,[13] although other studies have been carried out since that time.[14,15,16] Our study found that family practice is primarily the practice of medicine and pediatrics rather than surgery, obstetrics-gynecology and psychiatry. Almost all family practitioners use some form of diagnostic studies in addition to routine examination procedures. One half the survey sample reported they did some office x-ray work. Other than routine urinalysis, electrocardiograms and complete cell blood counts, little in the form of diagnostic procedures is utilized by the typical practitioner.

Most practitioners perform biopsy, tonsillectomy and adenoidectomy and dilatation and curettage but tend to refer their patients to specialists when a larger procedure is called for. (Family practitioners typically assist in the operations in those cases.) Perhaps, more time spent in the practice of assisting rather than doing these procedures would be of benefit in residency training.

Approximately one-third of all those physicians surveyed do not practice obstetrics. In contrast we found a large involvement by family practitioners in personal counseling of patients. Again, this information might be considered in apportioning training time.

While physicians may be willing to refer acutely ill patients because of a need for a diagnostic or treatment skill, more encouragement might be needed where the issue concerns referral of chronic disease patients for rehabilitation. Reticence occurs, according to one investigator,[11] because of the need to surrender treatment of the patient to a non-physician. Without specific experience to help us learn that teamwork is required, we are likely to retain unaccepting attitudes in our referrals to community health team workers. Wylie[17] found while studying referral practices of physicians in the Baltimore, Maryland, area that 54 percent of a group of general practitioners did not refer even one stroke patient during the period from 1956 to 1964 to an existing inpatient rehabilitation center.

No one believes that all physicians entering family practice are alike, yet there has been little investigation into whether or not all family practitioners tend to be involved in essentially the same types of practice activities. Our study shows two patterns of practice, although there may be many more.[18,19] Since the concept of a family practice is one of inclusion, how do such varied patterns fulfill this criterion? The role of the family practitioner is one of function as well as of content so that all of these practitioners could serve as the primary physician to the patient. In fact, a special interest in one area of the medical spectrum would tend to give the physician a feeling of grasp in that field. One family practice residency program arranges for fellowships in the last year of training much as is done in other residencies.[11]

We are seeing a period of transition from general practice in all its varied forms, to the new family practice model which is much better defined. The new physician entering practice will have a clearer expectation of the family practice role. In this way he will realize that the special skills of continuing patient care make him a specialist in every way.

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MYOCARDIAL INFARCT AND VPB'S

If a patient with myocardial infarct exhibits multiple ventricular premature beats (VPB's), 10 to 15 per minute, unifocal, but they don't intercept the vulnerable period, would you allow this to continue and not be concerned or would you treat?

The setting has to be defined. If the patient had an acute myocardial infarction a few hours ago, if he has many ventricular ectopic beats, I think he ought to be treated, irrespective of where the beats fall. Because in effect if you have a policy that begins to accept certain ones, you have already opened up a potential Pandora's box. Paramedical personnel are frequently carrying out your instructions. When we compare nurses' monitoring with automatic analog devices or computers, we find that nurses pick up about 30 percent of events. Furthermore nurses miss early and multifocal events; they miss almost all of them. So if you lay down a policy merely based on certain types of VPB's, the nurse busy in a coronary care unit is likely to miss them. In effect it's better to have a policy of treating them all, though it's recognized that many of them are not hazardous.

—BERNARD LOWN, M.D., Boston
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Information

CLINICAL CARDIOLOGY SERIES

Cardiac Tamponade and Constrictive Pericarditis

Part II—Treatment

Ralph Shabetai, M.D.

Material Supplied by the American Heart Association

In the preceding article in this series, pathophysiology, clinical signs and symptoms, and etiologic feature of cardiac tamponade due to pericardial effusion and constrictive pericarditis were discussed. We shall now consider treatment of these conditions.

Tamponade

The only treatment for tamponade is removal of the fluid. If the patient is moribund, pericardiocentesis is carried out as an emergency measure. More often, the patient should be moved to the operating suite, intensive care area or cardiac catheterization laboratory. Of the several approaches to the pericardium, the xiphisternal is the safest. The patient rests supine with the thorax elevated 45 degrees. The skin and subcutaneous tissues a few mm from the xiphisternum are cleansed and infiltrated, and then pierced with the tip of a No. 11 blade. An 18T needle is advanced posteriorly until its tip has negotiated the bony margin of the thorax. The needle is then advanced close to the midline with a slight posterior tilt, until the pericardium is reached. If there is much effusion, little or no cardiac pulsation will be felt. The needle is advanced through the pericardium, usually with a palpable sensation.

A conventional electrocardiogram lead should be monitored throughout the procedure. If it is absolutely certain that all equipment is properly grounded, the position of the needle tip can be monitored by a direct ECG lead. A cable connects the needle hub and an indifferent electrode (for example, a limb lead) to the electrocardiograph which is set in position "V." If the needle tip touches the epicardium a large ST segment elevation occurs in the needle lead, and a smaller one in the conventional lead. Also ventricular extrasystoles may be provoked. When these phenomena occur, the needle should not be advanced further, but should be withdrawn slowly and carefully until the ST segments are again isoelectric.

As soon as the pericardium is entered, a specimen is aspirated; and if it is bloody, its hematocrit and clotting time are compared with these features of the patient's blood. Hemorrhagic fluid rarely clots and almost always has a lower hematocrit than venous blood. Pericardial pressure should then be measured with a manometer, after which specimens should be obtained for bacteriologic, chemical and cytologic studies. Removal of the first 50 to 200 ml of fluid usually produces prompt relief because of the steep pericardial pressure volume curve. Venous pressure and pulsus paradoxus decrease and the arterial pulses become full. Pericardial fluid is aspirated as long as it can be withdrawn easily, and preferably until the pericardial pressure is zero or less. No elaborate precautions to prevent air aspiration are needed; indeed, introduction of a volume of air or CO_2 equal to less than half the aspirated fluid volume is useful to delineate the pericardium in subsequent chest roentgenographs.

Sometimes it is desirable to leave a small tube in the pericardium. Chemotherapeutic agents may be instilled into the pericardial sac. A chest roentgenograph is obtained at the end of the procedure. Appropriate systemic antibiotic therapy is commenced, and if tuberculosis is a reasonable possibility, steroids may be administered as well.

If a delay in initiating pericardiocentesis is inevitable, the circulation can be temporarily sustained by infusion of isoproterenol together with volume expansion by means of dextran blood or saline solution. Isoproterenol is started at 2 to 4 micrograms per minute and increased until perceptible effects on the pulse and pressure are

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Part II of a two-part article. Part I appeared in the August issue.

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evident. Recurrence of tamponade may require repetition of pericardiocentesis, but surgical drainage may then be preferable. In traumatic cases, recurrence after one or two successful aspirations is an indication for surgical drainage. When tissue diagnosis is important and a physician experienced in the technique of pericardiocentesis is not available, the pericardium can simply be drained and a biopsy specimen taken under local anesthesia after excision of the xiphoid process.

Constrictive Pericarditis

Once a diagnosis of constrictive pericarditis is established, the patient should be referred to a thoracic surgeon for pericardiectomy. Patients improve following digitalization because of the frequent myocardial involvement associated with the constriction. Tachycardia secondary to atrial fibrillation responds well to digitalis, as in heart failure. These measures alone produce diuresis, but it is usually advisable to administer diuretic agents as well. These are given in high dosage for as long as they are effective and serum sodium and chloride levels are not excessively depressed. Serum potassium must be maintained at normal levels by means of oral potassium chloride administration, and salt intake should be moderately reduced. Because of liver congestion, alcohol and other hepatic toxins must be forbidden. These measures may be employed to effect an immediate improvement and to prepare the patient for pericardiectomy. They are also remarkably successful for variable periods in patients who are unwilling to undergo operation, but in these circumstances slow progression of physiologic decompensation invariably occurs.

Pericardiectomy is now a safe operation. In a young person without pericardial calcification, cardiac enlargement, or atrial fibrillation the mortality is virtually zero. Thus the operation is urgently indicated in subacute constrictive pericarditis. In chronic calcific constrictive pericarditis, the operative risk with experienced cardiac surgeons is 5 to 10 percent. Pericardiectomy is not an open heart procedure, but full cardiopulmonary bypass facilities should be immediately available to deal with cardiac trauma, evidence of which may appear suddenly at any time during the operation.

Several months elapse after operation before recovery is complete, especially in the more chronic cases. Venous pressure is reduced somewhat immediately following operation but only slowly returns to normal. Digitalis and diuretic agents may be required for several months to control edema and effusions. In the most chronic cases with heavy calcification and long standing congestion, the aim is improvement rather than cure. The results in such cases are limited by myocardial involvement, hepatic insufficiency, chronic pulmonary congestion and pleural disease.

Cardiac compression secondary to malignant disease should be managed as conservatively as possible. Pericardiocentesis and the instillation of cancer chemotherapeutic agents may control the process in some patients. In others it may be necessary to construct a pericardiopleural window to drain the pericardium via the pleural space. There is little to be done for patients with constrictive pericarditis secondary to malignant disease without an element of pericardial effusion. Surgeons are generally appropriately reluctant to perform pericardiectomy in such circumstances.

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More to come in the December issue of **California Medicine.**

Refer to: Poth JL, Johnson PK, George RP Jr., et al: Therapy of acute myelocytic leukemia—Daunomycin contrasted with a combination of cytosine arabinoside and 6-thioguanine. Calif Med 117: 1-11, Dec 1972

California Medicine
THE WESTERN JOURNAL OF MEDICINE

Therapy of Acute Myelocytic Leukemia

Daunomycin Contrasted with a Combination of Cytosine Arabinoside and 6-Thioguanine

JAMES L. POTH, M.D., PAUL K. JOHNSON, M.D., RALPH P. GEORGE, JR., M.D., AND STANLEY L. SCHRIER, M.D., *Stanford*

■ *Twenty-three patients with acute myelocytic leukemia (AML) were treated with daunomycin and the results contrasted to those obtained in a subsequent group of 18 patients treated with cytosine arabinoside (Ara-C) and 6-thioguanine (TG). The complete remission (CR) rate with daunomycin was 17 percent (mean duration 10.6 months) and the partial remission (PR) rate 26 percent (mean duration 44 days). Corresponding figures in the Ara-C and TG group were: CR rate 44 percent (mean duration 5.8 months) and PR rate 17 percent (mean duration 48 days).*

There were 12 deaths resulting from daunomycin-induced pancytopenia and in ten of the patients who died persistent leukemia infiltrate was found in antemortem marrow specimens or at autopsy. This contrasts with death of six patients from Ara-C and TG-induced pancytopenia, in four of whom residual leukemic infiltrate was not evident.

Daunomycin alone is deemed not suitable for induction of remission in AML. The results obtained with Ara-C and TG are encouraging and may be improved if the number of infectious deaths associated with drug-induced pancytopenia can be reduced.

This work was supported by the Hematology Training Grant, NIH T1 AM 5239 and the Tommy O. Prescott Fund.

Submitted January 13, 1972.

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planned [illegible]

THE USE OF NEW CHEMOTHERAPEUTIC agents, singly or in combination, has improved the remission rate obtained in acute myelocytic leukemia (AML). Early encouraging complete remission (CR) rates were reported with the use of daunomycin, an antibiotic in the anthracycline group.[1] Current evidence indicates that it acts by interfering with both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) metabolism.[2] Bernard et al[3] and Boiron et al[4] reported approximately 50 percent CR rates with use of daunomycin in AML, although a later cooperative European study[5] noted only a 25 percent CR rate in 71 patients so treated. In this country, Serpick and Wiernick[6] noted CR in 11 of 21 patients treated with daunomycin. Common to all these studies was a high incidence of drug related toxicity.

Arabinosyl cytosine (Ara-C), a cell-cycle specific analog of cytidine, was reported to induce remission in 25 percent of 118 patients with AML.[7] The use of other drugs with Ara-C has enhanced its effectiveness. Gee, Yu and Clarkson,[8] using Ara-C in combination with the purine analog 6-thioguanine (TG), obtained a CR rate of 42 percent in 36 evaluable patients with AML. A comparative study involving 227 evaluable patients with AML by Carey[9] revealed total remission rates (no distinction was made between complete and partial) of 16 percent with Ara-C alone,[6] 50 percent with Ara-C and TG, 32 percent with Ara-C and 6-mercaptopurine (6-MP), and 36 percent with Ara-C and daunomycin. Bodey, Rodriquez and Hart[10] obtained CR in 38 percent of 29 patients with AML employing Ara-C and cyclophosphamide. Finally, Ara-C in combination with cyclophosphamide, oncovin and prednisone (COAP) induced an overall CR rate of 39 percent in 33 patients with AML,[11] and the CR rate approached 75 percent in younger patients.

This report describes the results obtained using daunomycin alone, and Ara-C and TG, in two separate, successive groups of patients with AML.

Methods and Materials

From December 1, 1968, to November 15, 1969, 23 successive, unselected patients with AML, 15 male and 8 female, aged 14 to 74, were treated with daunomycin (Table 1). The drug was obtained through the Cancer Chemotherapy National Service Center of the National Cancer Institute. The 20 mg contents of each vial were diluted with normal saline solution and injected rapidly intravenously. One course of treatment consisted of 240 to 300 mg per square meter of body surface given over four or five days. If a bone marrow specimen ten days to two weeks after completion of the first course of daunomycin revealed persistence of leukemic infiltrate, a repeat course was given in an attempt to achieve marrow aplasia. Bone marrow aplasia was ascertained on marrow aspirate, or closed biopsy was performed with a Westerman-Jensen needle if necessary, and aplastic marrows had histiocytes, plasma cells, lymphocytes and less than 5 percent blast cells.

Ara-C, 3 mg per kg of body weight, and TG, 2.5 mg per kg, were administered to a successive group of 18 unselected patients with AML, seven men and 11 women aged 18 to 64 years. The drugs were given 10 to 12 hours apart, TG orally in the morning and Ara-C in the evening by rapid intravenous injection. In four patients with disease poorly responsive to daily therapy, both drugs were administered every 12 hours as indicated in Tables 2 and 3. The drugs were continued until myeloblasts disappeared from the peripheral smear. Further therapy was given until marrow aplasia was obtained. During this latter period, the bone marrow was examined every two or three days.

Initial studies in both groups included bone marrow examination, stool guaiac, complete blood count, platelet count, blood urea nitrogen, serum creatinine, urine analysis, serum uric acid, liver function tests, serum calcium and phosphorus, coagulation parameters (partial thromboplastin time, prothrombin time, and euglobulin clot lysis time), electrocardiogram, and chest x-ray. During administration of chemotherapy daily complete blood counts and platelet counts were obtained; liver function tests, serum creatinine and serum uric acid were obtained twice weekly. Electrocardiograms were obtained in the daunomycin group every 10 to 14 days.

The response to therapy was based on the criteria established by the Midwest Cooperative Chemotherapy Study Group.[12] Criteria for complete remission included M-1 marrow (5 percent or less blast cells with normal erythropoiesis, granulopoiesis and megakaryopoiesis), H-1 hemogram (hemoglobin more than 12 gm per 100 ml, neutrophil granulocyte count more than 1500 per cu mm, no blasts evident and a platelet count greater than 100,000 per cu mm). In addition, normal physical activity (S-1) and physical examination (P-1) were required. The patients classified as having partial remission had M-2 marrows (6 to 25 percent blast cells with normal erythropoiesis, granulopoieses and megakarypoiesis comprising the remaining marrow elements), H-2 hemograms due to hemoglobins less than 12 gm per 100 ml and occasional blasts on peripheral blood smear, but P-1 and S-1 ratings. Complete remission generally was considered to begin when M-1 and H-1 ratings were obtained and to have ended upon appearance of blasts on peripheral blood smear or reappearance of leukemic infiltrate in the bone marrow. Partial remission began when granulocyte and platelet counts were above 1500 per cu mm and 100,000 cu mm respectively, and was usually considered to end when, in the face of progressive disease, counts dropped below these levels.

All patients were treated on a general medical ward with coverage usually provided by the Stanford University Medical House Staff. Protective isolation, gut sterilization, and white blood cell transfusions were not employed. Platelet concentrates were administered when patients had platelet counts below 10,000 per cu mm or exhibited hemorrhagic manifestations. Packed red blood cell transfusions were given as indicated. Onset of fever over 38.5° to 39° C (101.3 to 102.2° F) was evaluated thoroughly and usually was treated with broad antibiotic coverage, generally including gentamacin or kanamycin and cephalothin or methicillin. Allopurinol was administered as indicated for hyperuricemia.

Maintenance therapy with 6-MP, 50 to 100 mg a day, and methotrexate, 20 to 30 mg intramuscularly weekly, was begun in patients entering remission when the granulocyte count exceeded 1500 per cu mm and the platelet count, 100,000 per cu mm.

The clinical information and results of therapy for the daunomycin treated patients are detailed in Table 1 and for the Ara-C and TG group, in Table 2. Four of the 23 patients treated with daunomycin entered CR (17 percent). The mean dose of drug necessary to obtain marrow aplasia in this group was 337 mg per square meter (the range was 60 to 480 mg/M^2). In one patient (Case 10, Table 1), acute tubular necrosis in the setting of E. coli sepsis and shock developed following one dose of daunomycin. She subsequently entered remission without further chemotherapy. The mean duration of complete remission was 10.6 months; median 10.2 months, (range 4 to 18 months). Three of the complete responders relapsed; only one (Case 2), was retreated with daunomycin and had no marrow response to 480 mg/M^2 in the final stages of her disease.

Partial remission was obtained in an additional six patients (26 percent). The mean dose of daunomycin required for marrow aplasia in this group was 300 mg/M^2 (240 to 480 mg/M^2). The mean duration of remission was 44 days, median 36 days, range 6 to 109 days. Upon relapse, two of these patients (Cases 3 and 4) responded to daunomycin a second time after 400 and 240 mg/M^2 respectively. Neither received a daunomycin when they relapsed again. The other four patients were not retreated with daunomycin upon relapse.

Eight of 18 patients treated with Ara-C and TG entered CR (44 percent) and an additional three achieved PR (17 percent). The complete remission in one patient (Case 3) may have been due in part to a preceding dose of daunomycin, 240 mg/M^2. Though there was no marrow response to the daunomycin, the drug may have altered the numbers of leukemic cells enough to have had a favorable influence on subsequent induction with Ara-C and TG. The mean number of doses of Ara-C and TG required for marrow aplasia in the responsive group was 21. (The range was from 5 to 48 doses and the mean total dose of Ara-C was 63 mg per kg.) In the seven patients not responding to therapy, five reached marrow aplasia after an average of 32 doses of drugs (range 20 to 49); mean total dose of Ara-C 96 mg per kg). Only one of the responsive group (Case 2) experienced recurrent leukemic infiltrate as the bone marrow recovered from aplasia and a second eight-day course of therapy was required to enter partial remission.

The mean length of complete remission in patients who relapsed was 5.8 months (median 3.0 months, range 1 to 13 months) and one patient (Case 7) continues in remission after 12 months. As was true in the daunomycin treated patients, partial remissions were of short duration, averaging 48 days (median 54 days, range 30 to 60 days).

TABLE 1.—*Data on Patients Treated with Daunomycin*

Patient Age/Sex	WBC/mm^3 at Initiation of Therapy with Daunomycin	% Blasts	Platelets/mm^3 at Initiation of Therapy	Previous Therapy	Total Dose Daunomycin (mg/m^2) For Initial Remission Attempt	Duration and Type Remission	Survival (Months) Total	Survival (Months) After Initiation Daunomycin	Current Status
RESPONDERS									
1. 71/F	56,000	24	80,000	No response with 6-MP for one month	330	CR 4 mo.	7	6	Died in relapse elsewhere with E. coli sepsis.
2. 26/F	10,800	58	228,000	0	480	CR 15 mo.	24	23	Partial remission with Ara-C and TG.
3. 43/M	23,000	24	85,000	0	240	PR 22 days	6	5.5	Second PR (28 days) after additional 400 mg/M^2 daunomycin. Died of intracerebral hemorrhage upon relapse.
4. 49/F	8,700	25	155,000	0	240	PR 20 days	8	8	Second PR after additional 240 mg daunomycin. Upon relapse, no marrow response to 240 mg/M^2 daunomycin, died with uncontrolled leukemia.
5. 52/M	9,000	20	4,000	0	480	PR 109 days	9	9	Partial remission with Ara-C and TG.
6. 35/M	5,000	16	5,000	0	480	CR 18 mo.	20	20+	Currently in complete remission.
7. 18/F	1,200	30	23,000	No response to 6-MP for 4 weeks	360	PR 50 days	8	5	No response with Ara-C and TG, died of leukostasis.
8. 74/M	159,000	72	12,000	0	240	PR 6 days	21 days	17 days	Patient died with pseudomonas sepsis, M-1 marrow, 1500 granulocytes/mm^3.
9. 49/M	13,600	20	12,000	0	240	PR 56 days	4	3	Patient died with staphylcoccal pneumonia after 7 days Ara-C and TG.
10. 24/F	93,000	91	17,000	0	60	CR 5.5 mos.	10	10+	Complete remission with Ara-C and TG.
NONRESPONDERS									
11. 29/M	65,000	53	15,000	Partial response to 6-MP	240	0	4	1	Patient died with pseudomonas sepsis. At autopsy marrow infiltrated with leukemia.

12.	19/M	1,700	25	45,000	Partial response to 6-MP	240	0	15	1	Patient died with pseudomonas sepsis, antemortem marrow infiltrated with leukemia.
13.	26/M	45,000	50	80,000	Partial response to vincristine-prednisone	240	0	13	1	Patient died with E. coli sepsis. At autopsy extensive organ involvement with leukemia.
14.	34/F	109,000	65	12,000	Partial response to 6-MP	240	0	7	1	Died presumed sepsis, antemortem marrow aplastic.
15.	71/M	21,000	75	55,000	0	240	0	18	15	Died with probable sepsis; marrow infiltrated with leukemia at autopsy.
16.	52/M	4,700	45	60,000	No response to 6-MP	300	0	5	1	Died with pneumonia organism undetermined; antemortem marrow infiltrated with leukemia.
17.	43/M	5,000	38	15,000	0	420	0	1	1	Died with pneumonia organism undetermined; antemortem marrow infiltrated with leukemia.
18.	14/M	1,000	68	4,000	No response to vincristine-prednisone	240	0	5	5	Died pseudomonas sepsis; at autopsy no evidence of leukemia.
19.	20/M	13,000	70	13,000	Partial response to 6 courses Ara-C alone given elsewhere	480	0	15	4	Died uncontrolled leukemia; no marrow response with daunomycin.
20.	45/F	45,000	60	129,000	0	120	0	20 days	10 days	Died from central nervous system hemorrhage and at autopsy extensive leukemic infiltration present.
21.	19/M	124,000	93	20,000	0	300	0	1	1	Died from presumed sepsis. At autopsy marrow aplastic, testicular infiltration with leukemia.
22.	71/F	51,000	70	45,000	0	600	0	1.5	1	Died from presumed sepsis, antemortem marrow infiltrated with leukemia.
23.	60/M	480	5	20,000	0	600	0	1	1	Died from generalized candida albicans infection. At autopsy no evidence of leukemia.

+*Still alive*

TABLE 2.—*Data on Patient Treated with* ARA-C *and* TG

Patient Age/Sex	*WBC/mm³ at Initiation of Therapy with* ARA-C *and* TG	*% Blasts*	*Platelets/mm³ at Initiation of Therapy*	*Previous Therapy*	*Total Number of Doses Required for Marrow Aplasia*	*Duration and Type Remission*	*Survival (Months)*		*Current Status*
							Total	*After Initiation* ARA-C *and* TG	
RESPONDERS									
1. 21/F	114,000	80	85,000	0	39	CR 5 mo.	7	7$^+$	Partial response to 50 doses ARA-C and TG after initial relapse.
2. 26/F	1,500	5	220,000	15 mos. CR after daunomycin	13 8*	PR 54 days	24	8	Partial response to two courses of COAP (2 mo.); subsequently no marrow response to 480 mg daunomycin. Patient died from uncontrolled leukemia.
3. 54/F	1,400	5	147,000	Patient received 240 mg daunomycin with no marrow response (counts are prior to daunomycin)	11	CR 13 mo.	15	14.5	Reinduction failure.
4. 52/M	800	50	50,000	109 day PR after daunomycin	10	PR 60 days	12	3	Died of E. coli sepsis during attempt to reinduce remission (5 doses ARA-C and TG). No autopsy done.
5. 57/F	36,000	50	50,000	0	16	CR 3 mo.	5	3.5	Died elsewhere in relapse of presumed sepsis, reinduction was not attempted.
6. 56/F	1,600	10	157,000	0	5	CR 10 mo.	13.5	13$^+$	Currently partial remission (60 days).
7. 44/F	1,100	30	106,000	0	16	CR 12 mo.	13	13$^+$	Currently in complete remission.
8. 64/F	1,900	5	18,000	6 month CR with 6-MP	13	CR 3 mo.	17	6$^+$	Patient in complete remission (60 days) after successful reinduction.
9. 19/M	77,000	90	11,000	0	31	CR 1 mo.	3	3$^+$	Currently in PR after two doses COAP.

10.	60/M	117,000	95	13,000	0 One year course consistent with indolent leukemia.	26	PR 1 mo.	14	3	Died elsewhere of leukostasis. Reinduction not attempted.
11.	24/F	4,200	0‡	300,000	5.5 mo CR after daunomycin	48 (last 24 doses given every 12 hrs)	CR 1 mo.	9	3.5^{+}	Currently in complete remission.
NONRESPONDERS										
12.	18/F	10,000	90	10,000	50 day PR after daunomycin	30	None	8	2	Marrow aplasia followed by rapid return of leukemic infiltrate. Patient died of leukostasis.
13.	55/M	3,600	50	12,000	56 day PR after daunomycin	7 (aplasia not achieved)	None	4	10 days	Died of staphylococcal pneumonia during induction. At autopsy heavy organ infiltration with leukemia.
14.	61/F	21,000	96	98,000	0	33	None	1.5	1.5	Died of E. coli sepsis during period of marrow aplasia. At autopsy no evidence of leukemia.
15.	50/M	144,000	95	21,000	0	20	None	1	1	Died with presumed sepsis during period of marrow aplasia. No autopsy.
16.	64/F	7,000	80	10,000	0	49 last 14 doses given every 12 hrs.	None	2	2	Died with enterobacter bacteremia during period of marrow aplasia. No autopsy done.
17.	41/M	8,800	43	76,000	0	44 (aplasia not achieved)	None	2	1.5	Died from pseudomonas pneumonia while on therapy. At autopsy organ infiltration with leukemia.
18.	39/M	4,200	5	250,000	6 week partial response to vincristine and prednisone	28	None	3.5	1.5	Died from pseudomonas sepsis during period of marrow aplasia. At autopsy no evidence of leukemia present.

+Still alive

**Required two courses of therapy to marrow aplasia before remission obtained*

‡Marrow infiltrated with myeloblasts

TABLE 3.—*Data on Patients in Whom a Second Reinduction with Ara-C and TG was Attempted*

Patient Age/Sex	Total Doses Required for Initial Induction	Duration and Type of Initial Remission	Total Doses Ara-c and tg Administered During Reinduction Attempt	Result of Reinduction Attempt
1. 21/F	39	cr 5 mo	50 Given every 12 hours	Currently in pr (30 days). Maintenance—7 doses Ara-c and tg every 3-4 weeks.
2. 54/F	11 + 240 mg/M² daunomycin	cr 13 mo	42 Given every 12 hours	Patient died of pulmonary embolus. Autopsy—marrow aplastic but leukemic infiltration of gastric wall present.
3. 56/F	5	cr 10 mo	6	Currently in pr (80 days). Maintenance—3 doses Ara-c and tg every 5-6 weeks.
4. 64/F	13	cr 3 mo	10	Currently in cr (60 days); given 6-mp and methotrexate for maintenance.
5. 52/M	10	pr 2 mo	5	Died of E. coli sepsis during administration of Ara-c and tg before marrow aplasia obtained. No autopsy done.

Five of the Ara-c treated patients who relapsed were retreated by the initial induction method. The results of retreatment are given in Table 3. The two patients with initially easily controllable disease (just five doses of Ara-c was required for initial remission in Case 3, and Case 4 was responsive to 6-mp) were easily induced a second time. The other three patients whose disease initially required more vigorous chemotherapy, or who were never well controlled, either could not be induced a second time with Ara-c and tg, or (Case 1) obtained pr only after an arduous period of reinduction.

Patient age upon initiation of therapy did not prove to be a significant factor in determining response in either daunomycin or Ara-c and tg treated patients. The mean age of the daunomycin responsive group was 44 years (the median 46 years and the range 18 to 74 years). Corresponding figures in the Ara-c and tg responsive group were: mean 43 years, median 52 years and range 18 to 64 years. Contrasting ages in the daunomycin failures were: mean 39 years, median 50 years and range 14 to 71 years. The mean age of the seven Ara-c and tg failures was 47 years, the median 50 years and the range 18 to 64 years.

Previous therapy had an adverse effect on the outcome of therapy in patients receiving daunomycin. Only two of nine previously treated patients (22 percent) entered remission with daunomycin whereas the total remission rate in the 14 patients not previously treated was 57 percent and the cr rate 21 percent. This difference was not clearly evident in the group treated with Ara-c and tg, where five of eight patients (62 percent) having received previous chemotherapy, and six of ten patients (60 percent) not so treated, entered remission. However, inclusion of Patient 3, Table 2, who was initially treated with daunomycin, and Patient 8, Table 2, who had a complete remission with 6-mp, may bias the previous treatment group of patients receiving Ara-c and tg toward response. With these two patients excluded, the response rate in the previously treated group of Ara-c and tg patients was only 38 percent.

The median survivals for the two therapeutic groups of patients are shown in Table 4. The long median survival for the daunomycin complete responders is skewed by the small number of patients, and the fact that two unusually long survivals were seen (Case 2, 24 months, and Case 6, still alive at 20 months). Complete survival curves for the Ara-c and tg patient group cannot be determined because several of the responders are still living or have been in remission for only a few months.

TABLE 4.—*Median Survival (months) after Initiation of Therapy for all Patients in the Two Treatment Groups*

	Survival Daunomycin	*Patient Number*	*Survival Ara-C and TG*	*Patient Number*
Total Group	2.0	23	4.5	18
CR	24	4	12	8
PR	5.5	6	3.5	3
No Response	0.8	13	2	7

Toxicity

The consequences of drug-related pancytopenia, with granulocyte counts consistently below 500 per cu mm and platelet counts below 10,000 per cu mm, represented the major complication of therapy in both groups of patients. Following completion of one course of daunomycin, those patients responding endured an average of 13 days (range 7 to 20 days, median, 15 days) with granulocyte and platelet counts below 500 and 50,000 cu mm respectively. Those responsive patients who required two courses of daunomycin endured low granulocyte and platelet counts for an average of 55 days (range 45 to 60 days) following completion of their first course of drug. The average time from cessation of therapy in the responsive Ara-C group until recovery of granulocyte and platelet counts (above 500 and 50,000 cu mm respectively) was 20 days (range 10-47 days, median 25 days).

All patients became febrile during the pancytopenic period. Gram-negative bacteremia was the most common identifiable source of fever, and pseudomonas was isolated in seven instances. One case of fatal generalized candida albicans infection (Table 1, Case 23), was seen. Twelve patients died during periods of daunomycin-induced pancytopenia. The causes of death are included in Table 1. Only three of this group (Cases 14, 19 and 23), had aplastic bone marrow at autopsy, and one of these patients (Case 19) had leukemic testicular infiltration. In the other nine patients who died, despite profound pancytopenia, residual leukemic marrow infiltration was noted on antemortem marrow examination or at autopsy. This situation contrasts with that seen following Ara-C and TG. There were six deaths from infection (Table 2) during initial induction in this group of patients. Two of these patients (Cases 13 and 17) had leukemic infiltration of bone marrow and other organs at postmortem examination. The other four patients had aplastic bone marrows before death, and in the two cases in which autopsy was done no evidence of leukemia was found.

A syndrome encompassing clinical features generally seen in primary myocardial disease has been described following daunomycin therapy.[13] There were two instances of cardiac disturbance in our daunomycin-treated patients, neither clearly related to the drug. In one case (Case 4, in Table 1) transient, first-degree heart block occurred during a period of sepsis after 240 mg/M^2 of daunomycin but did not recur following further administration of the drug. A second patient (Case 6, Table 1) had paroxysmal atrial tachycardia during an episode of proteus mirabilis sepsis after 480 mg/M^2 daunomycin.

Hepatic or renal dysfunction clearly related to either daunomycin or Ara-C and TG was not observed although disturbances of these two organ systems were frequently seen during septic episodes. No autopsy evidence of drug related hepatic, renal or cardiac toxicity was seen in any patient so studied.

Reversible alopecia occurred in all patients surviving daunomycin-induced pancytopenia and in one patient (Case 6, Table 2) treated with Ara-C and TG. Oropharyngeal mucositis and oral ulcerations were noted in five patients treated with daunomycin and in four patients who received Ara-C and TG. Nausea and vomiting occurred within 12 hours of injection of Ara-C in roughly 20 percent of patients. Phenothiazines proved effective in averting this unpleasant side effect.

Discussion

Despite doses of daunomycin similar to those employed by other investigators,[3-6] we were unable to obtain a satisfactory number of complete remissions, noting a CR rate of only 17 percent (21 percent in previously untreated patients). Conceivably, minor differences in scheduling and dosage could contribute to our low complete response rate. For example, Serpick and Wiernik[6] gave repeated three-day courses of 60 mg/M^2 daunomycin until marrow aplasia was obtained. Inclusion of the six partial remissions increases the overall response rate with daunomycin to 43 percent. However, although in both the daunomycin and Ara-C and TG groups of patients, the favorable influence of CR on survival noted by other investigators[14-16] was evident, the effect of PR on survival was less clear. Also the duration of partial remissions in both treatment groups was short. These considerations suggest that, in our series, only CR should be used as a criterion of adequate response to therapy.

Other observers[3-6] have generally noted either remission or death during pancytopenia *with* bone marrow aplasia in patients treated with daunomycin. The presence of leukemic marrow infiltration in nine of our 12 fatalities in the daunomycin treated group, and testicular involvement in a tenth, is a distressing finding. It indicates that in our hands the rigors of daunomycin toxicity were often endured *without* the benefit of marrow aplasia and hence little chance of remission. Perhaps better results might be obtained by varying the schedule of administration to take advantage of the long plasma half-life of daunomycin (55 hours[17]) or by combination of daunomycin with other drugs such as Ara-C.[18] However, on the basis of our experience, we believe that administration of daunomycin alone in four or five day courses is not a suitable method for induction of remission in AML.

In contrast to the daunomycin experience, Ara-C and TG administered in a manner similar to that described by Gee, Yu and Clarkson[8] proved an effective method for induction of initial remission in AML. Our results differ from those of Gee et al only in that once marrow aplasia was obtained in responsive patients, with one exception, they entered remission as the marrow recovered. Fourteen of Gee's 19 responders required two or three courses of Ara-C and TG to bring about marrow hypoplasia, before remission was obtained. This difference loses some significance when one compares the total dose of Ara-C required for remission in our cases (mean 63 mg/kg, range 15 to 144 mg/kg) to that in Gee's series (mean 58 mg/kg, range 15 to 132 mg/kg). Our results suggest, then, that more vigorous therapy initially may circumvent the need for subsequent courses of drug.

The mean number of 25 days required to induce marrow aplasia in our patients treated with Ara-C is excessively long and has serious consequences in patient morale and in cost, as well as risk of infection. Further, patients failing on Ara-C and TG required larger amounts of chemotherapy to reach marrow aplasia (mean 32 days, mean total dose of Ara-C 96 mg/kg) than the responsive patients (mean 21 days, mean total dose of Ara-C 63 mg/kg). It is clear from the data of Bodey et al[19] that the hazard of infection parallels the duration of granulopenia in neutropenic patients. Reduction of the period required for induction of marrow aplasia appears to be a critical factor in management of patients at centers not having elaborate facilities to support granulopenic patients. In an effort to obtain shorter induction periods, Clarkson's group[20] has used twice-daily administration of Ara-C and TG in full dose. We used a similar schedule in patients proving resistant to daily drug administration (Tables 2 and 3). In addition to increased frequency of administration, combination of Ara-C with other drugs such as COAP*[12] or daunomycin[9,18] offers another approach to shorter induction periods.

The choice of therapy for those patients who relapse after initial remission with Ara-C and TG is not clear. While the number we treated was small, reinduction was arduous, and was successful in only one instance, for patients who required large amounts of chemotherapy for initial induction. It seems reasonable, in such patients, to attempt reinduction with a different combination of drugs, such as COAP.

The present experience with Ara-C and TG indicates that a general medical service with competent hematological and laboratory support can treat AML effectively with currently available agents. Though innovative approaches to acute leukemia, and new treatment protocols, belong in the realm of centers specializing in such endeavors, it appears that not all patients with leukemia should be treated at such centers. There is obvious merit in enabling a patient with devastating diseases such as AML to be treated relatively near his home.

On the basis of this experience, we believe daunomycin is not a suitable agent when used alone in four or five-day courses for induction of remission in AML. In contrast, Ara-C and TG offer a reasonably effective mode of therapy for this disease. Higher remission rates with Ara-C may be possible at centers with limited support facilities if a fraction of the infectious deaths now seen can be averted by shortening the period required for induction of bone marrow aplasia.

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*A combination of cytosine, vincristine sulfate (Oncovin®), cytosine arabosinoside and prednisone.

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GLAUCOMA A THREAT AFTER RETINAL DETACHMENT OPERATIONS

A patient who has had a retinal detachment successfully operated on remains a glaucoma candidate for life. I have seen a number of patients who were not followed for their ocular pressure or the possibility of glaucoma even a few months postoperatively and were allowed to lose all usable vision in the surgically treated eye by a gradual insidious glaucoma with relatively low tension. These patients, in my opinion, should be checked all through life at least twice a year for the possibility of tension abnormalities or glaucoma. I think this is a subject that has very important clinical implications for all of us because while we may not do retinal surgery or may not care to do it, all of us follow patients successfully operated on for retinal surgery. No check for glaucoma in these patients may mean blindness in a small number.

—CHARLES L. SCHEPENS, M.D., Boston
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Responses of Previously Reinfected Rubella Vaccinees to Challenge with Brown Strain Rubella Virus

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■ *The responses of seven* HPV-77 *rubella vaccinees to initial challenge with "wild" rubella virus have been compared with their responses to rechallenge with Brown strain rubella virus and to the responses of five "natural" immunes to initial Brown strain challenge. Previous exposure to "wild" rubella virus 220 days post vaccine-induced immunity had resulted in six of the seven vaccinees experiencing asymptomatic reinfection. On "rechallenge" none of the previously "reinfected vaccine immunes" demonstrated clinical, virologic or serologic evidence of reinfection. These data are consistent with the conclusion that persons with vaccine-induced immunity may be assured of more prolonged and solid immunity to rubella without having to suffer the clinical disease if they are reinfected with nonattenuated rubella virus. Rigidly controlled experiments, designed to study the practicality and safety of immunization with live rubella vaccine(s), followed by deliberate challenge of vaccinees with "wild" or low tissue culture passage rubella virus, seem warranted. In addition, these data indicate that it is imperative that a distinction should be made between "vaccine immunes" and previously "reinfected vaccine immunes" in any evaluation of long term rubella vaccine(s) efficacy and vaccine-induced antibody decay.*

IT IS RECOGNIZED that as many as 80 percent of persons who have rubella antibodies induced by one of the live rubella vaccines, may experience asymptomatic reinfection upon challenge.[1-4] Such challenge may occur subsequent to exposure to patients with naturally acquired "wild virus" induced rubella, or as a consequence of artificial challenge by intranasal instillation of a laboratory-grown, non-attenuated rubella virus such as the "Brown" strain.[1-4] These high reinfection rates, despite vaccine-inducted antibodies, contrast sharply with the reported less than 5 percent reinfection rate among persons whose original rubella antibodies have been engendered by

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previous infection with naturally transmitted "wild" rubella virus.[1] Thus, it has been suggested that, regarding the prevention of asymptomatic reinfection, there may be a qualitative, as well as a quantitative difference between the immunity following immunization with currently available live rubella virus vaccines and that which follows naturally acquired infection with "wild" rubella virus.[1,2]

With these high asymptomatic reinfection rates among vaccinees after initial challenge, it seemed important to gain expanded information about the rubella immunity among vaccinees who have had previous reinfection with "wild" rubella virus, and to contrast their rubella immunity to immunity among persons whose entire previous antigenic experience with rubella had been due to infection with "wild" rubella virus. To achieve this comparison, seven children whose first rubella antibodies had followed injection of the HPV-77 live rubella virus vaccine, and who had had subsequent serologic evidence of reinfection with "wild" rubella virus were "rechallenged" by intranasal instillation of the Brown strain of rubella virus. The responses of these "previously reinfected vaccinees" to Brown strain challenge one year after reinfection were compared with the responses of five children who were "natural immunes"—that is, they had never received live rubella virus vaccine and had acquired their rubella immunity by laboratory confirmed natural rubella infection one year previously.

Materials and Methods

Subject Selection. The study group consisted of 12 mentally retarded children from the population at Pacific State Hospital, Pomona, California. The 12 children (seven boys, five girls) ranged in ages from five years four months to thirteen years five months, with a median age of ten years. Six of the 12 children had Down's syndrome. All were ambulatory. The 12 children were originally members of a group of 15 volunteer participants in studies of live rubella virus vaccines and vaccine-induced immunity among children in an isolation ward and were part of Study Group 2 in our original report.[2] The experimental designs, serologic and virologic responses of Study Group 2 to HPV-77 vaccine administration and first challenge by exposure to "wild" rubella virus have been reported in detail.[2] Of the 12 children, seven belonged to the cohort of eight who had been challenged one year previously by exposure to naturally acquired, clinically evident rubella. This challenge occurred 220 days subsequent to the administration of HPV-77 vaccine with development of vaccine-induced antibodies. At the time of this initial challenge, six of the seven children had serologic evidence of asymptomatic reinfection and rubella virus was isolated from the pharynges in two (Nos. 7039, 7009).[2]

The remaining five children had "wild" virus-induced immunity and originally served as transmission contact controls for the HPV-77 vaccine efficacy trials of Group 2 and had remained susceptible* to rubella despite close contact with vaccinees.[2] Some 220 days following the beginning of the original efficacy trials, one of the susceptible children was accidentally exposed to a laboratory confirmed case of natural rubella on her home ward.[2] This child served as the index case of natural rubella for the first challenge of the seven vaccinees discussed in this report and transmitted clinical rubella to the other four rubella-susceptible children. Therefore, following exposure to "wild" rubella virus, all five children had developed clinical, virologic and serologic evidence of rubella one year before the present study.[2]

Study Facility. For the rechallenge studies, all 12 children were admitted to a special isolation ward where clinical and virologic surveillance could be maintained under controlled conditions. This rubella study ward and its operation have been described in detail previously.[2]

Rechallenge Virus and Administration. The Brown strain of rubella virus, originally isolated from a recruit with rubella at Fort Dix, New Jersey, was employed as the challenge virus.†[3] The challenge material was stored at −70°C, transported on dry ice, and was thawed at Pacific State Hospital immediately before its administration.

The Brown strain challenge virus was administered by dropwise instillation of 0.5 ml into each nostril of all 12 children by means of a 1.0 ml tuberculin syringe. Thus, each child received 1.0 ml of the challenge virus—that is, $10^{4.1}$InD$_{50}$'s. Sneezing, coughing or vomiting did not occur in

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*Susceptible = rubella hemagglutination inhibition (HAI) antibody titer of less than 1:8.

†The challenge virus was in its fifth African Green Monkey Kidney (AGMK) tissue culture passage and was furnished to us after appropriate safety testing by Parke Davis & Company. The AGMK infectivity of this preparation, as determined in our laboratory was $10^{4.1}$ interfering doses$_{50}$(InD$_{50}$) per ml.

TABLE 1.—*Sampling Days for Detection of Rubella Virus Viremia*

Case Nos.	*Days Sampled Post-Challenge*
"Rechallenged Reinfected* Vaccine Immunes"	
7005	5, 6, 11, 12
7039	5, 6, 11, 12
7003	7, 8, 11, 12
7086	7, 8, 11, 12
7009	9, 10, 13, 14
7087	9, 10, 13, 14
7054	9, 10, 13, 14
Natural Immunes†	
7051	7, 8, 13, 14
7082	7, 8, 13, 14
7024	5, 6, 11, 12
7020	5, 6, 11, 12
7085	9, 10, 13, 14

*Original rubella antibodies induced by HPV-77 vaccine with subsequent evidence of reinfection upon challenge with "wild" strain rubella virus one year prior to the present "rechallenge" study.

†Original rubella antibodies induced by natural infection one year prior to the present "rechallenge" study.

any child during a two-minute observation period immediately after instillation of the challenge virus.

Clinical Surveillance and Specimen Collection. For a 30-day period immediately subsequent to rechallenge, all 12 children were examined daily by the senior author (J.W.) and temperatures, pulse and respiratory rates were recorded by the ward nursing staff.

All 12 children were monitored for virus excretion by throat and nasal swabs on days 0 to 30. Specimens on day 0 were obtained immediately before rechallenge with the Brown strain. Heparinized blood for attempts at virus isolation were collected on four days from each of the 12 children (Table 1). In addition, serum specimens for rubella antibody titrations were obtained from all children on day 0 and on days 15, 30, 60, 120 and 180 post-rechallenge.

Virologic Laboratory Methods. The rubella isolation and identification procedures described by Parkman et al were employed.[5] The veal infusion broth (VIB) extracts of the nasal and throat swabs and the slurries of whole blood samples were studied. After kaolin adsorption to remove non-specific inhibitors, serum samples were tested for rubella hemagglutination-inhibiting (HAI) and complement-fixing (CF) antibodies by microtiter techniques.[6-8] Serial serum specimens from each child were titrated in the same "run" to allow more precise detection of significant increases and decreases in the titers. Control sera with known rubella HAI and CF titers were included with each run, and all tests were repeated at least once to check the reproducibility of results.

Results

Clinical Findings After Rechallenge of Rubella Immunity with Brown Strain Virus. As anticipated, none of the 12 children (seven previously "reinfected immunes" and five "natural immunes") demonstrated signs or symptoms of clinical rubella during the 30-day observation period after rechallenge of their immunity with the Brown strain of rubella virus.

Virus Isolation Studies. Although nose and throat specimens for virus isolation were collected from each child daily for 30 days subsequent to rechallenge, none of the samples yielded rubella viruses when cultured in AGMK. Similarly, rubella virus was not isolated from any of the heparinized slurries of whole blood collected on four occasions from each child (Table 1).

In contrast, two other children classified as "HPV-80 vaccine failures,"* and *not* members of the group of 12 discussed here, were challenged simultaneously. Detailed results with these two children have been reported separately.[9] The two HPV-80 "vaccine failures" each shed rubella virus from the nose or throat or both, one on days 8 to 12 and the other on days 5 to 15, post Brown strain challenge.[9] This attests the infectiousness of the challenge virus.

Serologic Results Following Rechallenge. Consistent with the lack of clinical evidence of rubella and the results of the virus isolation studies, none of the seven "rechallenged" HPV-77 vaccinees nor any of the five "natural immunes" showed evidence of reinfection following intranasal challenge with the Brown strain of rubella virus as determined by HAI and CF serological methods (Tables 2 and 3).

One "rechallenged" HPV-77 vaccinee (No. 7005 in Table 2) is of particular interest. He had not shown serologic evidence of reinfection during the 60 days immediately subsequent to his initial challenge by exposure to "wild" rubella virus one year previously,[2] and during the current study he proved resistent to reinfection when his im-

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*A person who fails to develop detectable rubella antibodies after rubella vaccine(s) inoculation.

TABLE 2.—*Rubella HAI and CF Antibody Responses of HPV-77 Vaccinees to Intranasal Challenge with the Brown Strain of Rubella Virus ($10^{4.1}$InD$_{50}$) One Year Following Previous Challenge by Natural Rubella*

HPV-77 Vaccinees		Days Following Second Challenge 0	15	30	60	90	120	180
7009	HAI	256	512	512	512	128	256	128
	CF	8	8	8	8	8	8	8
7039	HAI	512	512	512	512	256	128	64
	CF	8	<8	<8	<8	<8	<8	<8
7005	HAI	256	512	512	N.D.*	256	256	128
	CF	<8	<8	<8	N.D.	<8	<8	<8
7087	HAI	16	16	16	16	8	8	8
	CF	8	<8	<8	<8	<8	<8	<8
7054	HAI	512	512	512	512	512	256	256
	CF	8	<8	<8	<8	<8	<8	<8
7086	HAI	256	256	256	256	256	256	256
	CF	<8	<8	<8	<8	<8	<8	<8
7003	HAI	128	128	128	128	128	128	128
	CF	<8	<8	<8	<8	<8	<8	<8

*Not Done

TABLE 3.—*Rubella HAI and CF Antibody Responses to Intranasal Challenge with the Brown Strain of Rubella Virus ($10^{4.1}$InD$_{50}$) One Year Following Natural Rubella*

Case Nos.		Subjects with Natural Rubella One Year Previously Days Post Challenge 0	15	30	60	90	120	180
7024	HAI	256	256	512	256	128	128	128
	CF	8	8	8	8	<8	<8	<8
7020	HAI	256	256	256	256	128	N.D.*	64
	CF	<8	<8	<8	<8	<8	N.D.	<8
7051	HAI	512	512	512	512	128	128	128
	CF	16	8	16	8	16	8	16
7082	HAI	512	512	1024	1024	512	128	N.D.
	CF	16	16	16	32	16	16	N.D.
7085	HAI	512	512	512	512	256	256	128
	CF	8	16	16	32	16	16	16

*Not Done

munity was rechallenged with the Brown strain. To permit easy, close scrutiny, the following HAI and CF antibody responses of Vaccinee No. 7005 are summarized in Table 4: 1) Response to HPV-77 vaccine inoculation; 2) Response to initial challenge with "wild" strain rubella virus by exposure to other children with rubella and 3) Response after "rechallenge" by intranasal inoculation of the Brown strain of rubella virus. While on his home ward, and before the present Brown strain challenge, Vaccinee No. 7005 had developed a 4-fold increase in rubella HAI antibody, which was not accompanied by a concomitant rise in CF antibody. It is likely that he had acquired a natural reinfection before the Brown strain challenge, either on his home ward, or while on pass outside the hospital confines.

Discussion

Numerous clinical observations, viral isolation, and serologic studies of rubella vaccinees who possessed appreciable levels of vaccine-induced HAI antibodies have well characterized the asymptomatic reinfection which frequently follows primary challenge with "wild" rubella virus.[1-4] Recently, low or absent concentrations of anti-rubella gamma A immunoglobulin (IGA) in nasopharyngeal secretions following the subcutaneous administration of rubella vaccine(s) have been implicated in the greater propensity for reinfection to occur in the face of vaccine-induced immunity than among "natural" immunes.[10] In this respect, the qualitative equivalence of rubella vaccine-induced immunity and the immunity en-

TABLE 4.—*Serologic Responses of Subject 7005 Following* HVP-77 *Rubella Virus Vaccine, Natural Rubella Virus and the Brown Strain of Rubella Virus* ($10^{4.1}InD_{50}$*'s*)

	Days Post HPV-77 *Inoculation*						
Antibody Type	*0*	*30*	*60*	*90*	*120*	*180*	*220*
HAI	*	256	256	256	512	128	64
CF	*	<8	<8	<8	<8	<8	<8
	Days Post Exposure to Natural Rubella						
	0	*30*	*60*	*90*	*120*	*180*	*1 year*
HAI	64	64	128	256	512	256	256
CF	<8	<8	<8	<8	<8	<8	<8
	Days Post Exposure to Brown Strain Virus						
	0	*15*	*30*	*60*	*90*	*120*	*180*
HAI	256	512	512	N.D.*	256	256	128
CF	*	<8	<8	N.D.	<8	<8	<8

*Not done.

gendered by natural infection in the prevention of reinfection has been questioned. In view of all these data, it was of interest to compare the responses of seven HPV-77 vaccinees to initial challenge with "wild" rubella virus with their responses following second challenge with Brown strain rubella virus and to the responses of five "natural" immunes to initial Brown strain challenge.

In studies reported previously,[2] within 60 days following initial challenge of their vaccine-induced immunity, 220 days after vaccination, by exposure to children with clinically evident "wild" rubella, six of the seven HPV-77 vaccinees had shown serologic evidence of reinfection, and two of these "reinfected vaccinees" had pharyngeal shedding of rubella virus.[2] Yet, during the present study, upon rechallenge, one year after initial challenge, none of the seven shed rubella virus, nor did they have clinical or serologic evidence of reinfection despite the fact that one child, No. 7087, had demonstrated HAI antibody decay to a level of 1:16 at the time of second challenge. It is noteworthy that, throughout all of our primary challenge studies of rubella immunity, all children (8 of 31) who had HAI antibody titers of 1:32 or less which had been induced by live attenuated rubella virus vaccines, had laboratory evidence of reinfection upon first challenge with Brown strain virus or exposure to children with clinically evident "wild" rubella virus infections.[11] However, it is of equal importance that none of the five "natural" immunes in the present study showed virus isolation, serologic, or clinical evidence of reinfection after a period of follow-up equal in length to those in which 46 percent of primarily challenged vaccinees in our previous studies,[2] and 80 percent of the initially challenged vaccinees studied by Horstmann et al[1] were reinfected during documented challenges.

The data from the present "rechallenge" study suggest that persons with vaccine-induced immunity may be assured a more prolonged and solid period of protection by infection with a non-attenuated rubella virus subsequent to immunization. Because of the increased protection afforded by infection with "wild" rubella virus, it is also apparent that a distinction should be made between "vaccine immunes" and previously "reinfected vaccine immunes" in any evaluations of long term rubella vaccine(s) efficacy and vaccine-induced antibody decay.

On balance, the data accrued to date show that available rubella vaccines do not provide the same degree of protection against future reinfection as natural rubella.[1-4] Rubella immunization programs ultimately aim at the prevention of fetal rubella and rubella embryopathy. Controlled challenge studies, performed for obvious reasons only in non-pregnant persons with vaccine-induced antibodies, have shown that reinfection is usually asymptomatic.[1-4] Epidemiologic studies in populations in which all rubella immunity was due to previous "wild" virus infection have shown that the risk of rubella embryopathy is very low among infants whose mothers have escaped clinical rubella during the first trimester of pregnancy.[6,12-14] The proof of the degree of protection afforded the fetus of women with vaccine-induced antibodies who have asymptomatic reinfection during the first trimester of pregnancy, must await accidental natural challenge, and the slow accretion of data by the surveillance process.

The precise future significance of reinfected vaccinees in the epidemiology of rubella in the community remains uncertain. There has been, as yet, no proved transmission of rubella virus from reinfected vaccinees.[2,3] However, data are limited. Although future studies may show that reinfected vaccinees constitute an epidemiologic hazard, accidental natural reinfection in the community may have a plus side. It would appear, from the present study, that the "qualitative" gap" between rubella vaccine-induced and natural immunity may be filled by chance reinfection of vaccinees by "wild" rubella virus strains circulating in the community. Indeed, all the above facts could be used to support rigidly controlled, experimental modification of the usual rubella vaccine regimen to include the deliberate intranasal challenge of vaccinees with a low passage rubella virus comparable to the Brown strain as early as 60 days post-inoculation. It should be emphasized that any such modification should be undertaken only as a controlled experiment, and we are not recommending general adoption of such a regimen. The further complexity and cost of such an approach in contrast to present established procedures is realized. It is recognized also that this modification could not be undertaken if reinfected "vaccine failures" prove to be infectious.[9] Better would be the development of a more immunogenic vaccine that would offer a more solid and prolonged protection against future reinfection.

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"RAW HAMBURGER" AT SIGMOIDOSCOPY

The diagnosis of ulcerative colitis is made at sigmoidoscopy. In the acute phase, the only definition I can give you is that the colon looks like hamburger, raw hamburger. It's a bloody mess. You usually can see pus, oozing, and open ulceration. Diagnosis is more difficult if you happen to examine the patient between acute exacerbations. In that case, he has more subtle findings, what we describe as granularity. The rectal mucosa which is normally smooth and "glisteny" has a "sand-papery" appearance, like little fine granules of sand. If you rub it with the end of the sigmoidoscope, it bleeds on contact. These are very suggestive findings. The only thing which looks like ulcerative colitis is amebiasis. You get a swab and have the pathologist look at it and see if he can find amoebae.

—Ramon R. Joseph, m.d., Ann Arbor
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Rifampin in the Treatment of Pulmonary Tuberculosis

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■ *Rifampin is a newer semi-synthetic derivative of rifamycin. Its advantages over other derivatives are good oral absorption, high blood levels, and slower excretion rate.*

Rifampin has been studied in 68 patients and results can be summarized as follows:

- *There has been no evidence of significant toxicity.*
- *In a randomized study of active tuberculosis patients who had not received prior chemotherapy, isoniazid-rifampin and isoniazid-aminosalicylic acid regimens were equally effective.*
- *In retreatment patients with active, positive tuberculosis, the regimen of isoniazid, rifampin, and ethambutol proved to be very effective, especially when the two latter drugs had not been used previously.*
- *In patients with pulmonary infections caused by atypical acid-fast bacilli, results varied with the organism isolated and the extent of disease.*

Rifampin is a potent, relatively non-toxic drug especially useful in the retreatment of pulmonary tuberculosis in patients who have never received this drug previously. There is little justification for its use in initial therapy except in rare cases.

RIFAMPIN IS A NEWER *semi-synthetic* N-methylpiperazine derivative of rifamycin sv, isolated from a strain of Streptomyces mediterranei in 1959 by Sensi and others.[1] More than 400 derivatives have been prepared from rifamycin, and rifampin has been found to be effective against tubercle bacilli and atypical mycobacteria *in vitro.*[2]

Clinical studies with patients having tuberculosis, have indicated significant therapeutic effect, with reports at the 27th Veterans Administration-Armed Forces Pulmonary Disease Research Conference by Gyselen et al[3] and Verbist and Gyselen.[4] The advantages of rifampin over other derivatives of rifamycin sv are good oral absorption, high blood levels, and slower excretion rate.

Rifampin is an orange-red crystalline powder, tasteless, and stable at room temperature. It is readily absorbed from the gastrointestinal tract

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and is excreted mainly by the kidney and liver, but also in sputum. The drug is better absorbed on an empty stomach, reaching a peak blood concentration between one and four hours after ingestion of 600 mg, with levels of 7 to 9.5 micrograms per milliliter—greatly in excess of the minimal inhibitory levels required for Mycobacterium tuberculosis.[5]

Methods

Patients with pulmonary disease caused by acid-fast bacilli were studied in four groups. All had evidence of either active pulmonary tuberculosis caused by niacin-positive organisms or of pulmonary disease caused by atypical niacin-negative acid-fast bacilli. Each patient received the examinations noted in Table 1. The items in Group B and D were first repeated weekly. With the absence of toxicity, they were repeated biweekly, and then subsequently monthly. Audiometric and ophthalmologic examinations were repeated monthly.

Dosage of drugs used was: isoniazid (INH) 300 mg once daily by mouth; aminosalicylic acid (PAS) 4 grams three times a day by mouth; streptomycin (SM) in variable dosage, but usually 1 gram daily intramuscularly for the first month, 1 gram three times weekly for the next month, and then 1 gram twice weekly for an additional month; ethambutol (EMB) 15 mg per kilogram of body weight, once daily by mouth; rifampin (RFP) 600 mg once daily by mouth, before breakfast.

Results

Data were analyzed in four groups:

A. *Toxicity*

Of the 68 patients receiving rifampin for variable lengths of time, only minor changes in the serum glutamic-oxalacetic-transaminase (SGOT) were noted in 10 percent of the patients. Using the Sequential Multiple Analyzer (Technicon), normal values for SGOT are up to 50 milliunits per ml. Seven patients had increases in SGOT, up to 100 milliunits per ml in three cases. Elevations persisted from one to three months. These figures do not differ from those for patients with tuberculosis receiving isoniazid-para-aminosalicylic acid (INH-PAS) regimens, and from non-tuberculous emphysema patients not receiving any anti-tuberculosis drugs. No other drug reactions were noted and therapy was not stopped because of toxicity in any patient.

TABLE 1.—***Examinations Performed Regarding Potential Toxicity***

A. History and physical examination

B. Complete blood count
Hematocrit
Sedimentation rate
Platelet count
Routine urinalysis

C. Audiometric examination
Ophthalmologic examination

D. Serum chlorides
carbon dioxide
potassium
sodium
urea nitrogen
glucose
calcium
phosphorus
uric acid
cholesterol
total protein
albumin
total bilirubin
alkaline phosphatase
lactic dehydrogenase (SLDH)
glutamic-oxalacetic-transaminase (SGOT)

B. *Initial Therapy of Patients with Active Pulmonary Tuberculosis.*

Fifty patients with niacin-positive tubercle bacilli in the sputum and no previous drug therapy were randomized between INH-RFP and INH-PAS. Ninety-two percent of the patients had sputum conversion after 16 weeks of therapy on either regimen. The median time for sputum conversion to occur with both regimens was one and one-half months. Duration of RFP usage varied from three to five months. RFP was discontinued after sputum conversion and before discharge from the hospital, and replaced by a standard anti-tuberculosis drug, usually PAS or EMB. Follow-up of these patients has been relatively brief and no comments are warranted concerning relapse rates.

C. *Retreatment Patients.*

Twenty-five patients with active pulmonary tuberculosis and positive sputum cultures with a history of previous treatment were placed on a regimen of isoniazid-ethambutol-rifampin (INH-EMB-RFP). Good results were secured, with 92 percent conversion rates after 16 weeks of therapy. This group included four patients who had had positive sputum cultures for tubercle bacilli intermittently for 18, 10, and 6 years, and one patient positive consistently for the previous 5 years, but it must be emphasized that none of these patients had received ethambutol or rifampin previously.

D. *Atypical Acid-Fast Infections*

1. *M. kansasii*

Because of the small number of patients, these cases were not randomized. Twelve patients did well on the INH-RFP regimen, as had 20 patients previously treated with various combinations of INH-PAS, INH-SM, INH-SM-EMB. In this small group, sputum conversion occurred in all of the patients.

2. *M. intracellulare (Battey)*

Only six patients were treated with INH-RFP-EMB. If the sputum concentrates were negative and only the cultures positive, results were good (two patients). Patients with extensive bilateral disease and positive sputum concentrates for acid-fast bacilli usually did poorly on the INH-RFP-EMB regimen, as they usually did with other regimens. Patients with Battey infections often require five or six drug regimens.

The above results in all of the groups must be considered preliminary in view of the relatively short period of follow-up observations (months rather than years).

Discussion

Nitti reported the use of rifampin alone with 49 patients having positive sputum, and indicated that this drug had antituberculosis activity equivalent to isoniazid, that rifampin was well tolerated and apparently non-toxic, but that rifampin used alone permitted development of bacterial resistance.[6]

A Belgian cooperative study involving 120 patients with advanced pulmonary tuberculosis and positive sputum concentrates for acid-fast bacilli, compared four regimens: rifampin-placebo, rifampin-isoniazid, rifampin-ethambutol, and isoniazid-ethambutol. The rifampin-isoniazid treatment yielded 100 percent sputum conversion with negative cultures after completion of 13 weeks of treatment, and was slightly more effective than the three other regimens. No toxicity to rifampin was noted.[7]

Raleigh has coordinated two Veterans Administration Cooperative Studies—one for retreatment patients with active tuberculosis using rifampin and ethambutol,[8] and the other involving patients with advanced, previously untreated pulmonary tuberculosis. In the latter study, three regimens were compared: isoniazid-streptomycin, isoniazid-rifampin, and streptomycin-rifampin. Preliminary observations indicate these to be equally effective with about 93 percent conversion rates after 26 weeks of therapy.

The Veterans Administration studies confirmed “that rifampin is a drug of very low toxicity and apparently of high efficiency.”[9] At recent meetings of the American Thoracic Society, Raleigh and Lester each described his experience with patients requiring retreatment for far advanced active pulmonary tuberculosis.[10,11] In the Veterans Administration Rifampin Retreatment Study, Raleigh[12] reported that sputum conversion occurred in 94 percent of 48 patients. Unfortunately, 20 percent of these patients relapsed within several months. Various clinical trials indicate that rifampin is an effective, virtually non-toxic drug useful in the treatment of tuberculosis, but its exact role is far from clear.

Indiscriminate use of rifampin in initial therapy will decrease greatly its usefulness, if retreatment or additional treatment is required later. In Great Britain, it is felt that there is little justification for use of rifampin in initial treatment except in rare cases of intolerance to other drugs,[13] and with this I fully agree. Although no significant toxicity was detected in this small group of patients, and in other series of cases, reports of occasional toxicity are well-documented, including hypersensitivity,[7] fatty liver,[10] hepatotoxicity,[11] and thrombocytopenia purpura.[11] An article in *Lancet* in 1969 noted: “More than a hundred reports have been published on the use of rifampicin [rifampin] in man. From all this evidence it can be accepted that the drug is remarkably free from toxicity. As it has mostly been given with other antituberculosis agents, side-effects due to rifampicin cannot with certainty be separated from those due to other drugs.”[14] An important disadvantage of RFP is its cost. The daily hospital cost (for 600 mg) per patient is $1.84, compared with daily costs of 0.4 of one cent for INH, 7 cents for PAS, and 27 to 36 cents for EMB. A 1 gram dose of streptomycin costs 10 cents.

The current Veterans Administration Cooperative Study No. 33 randomizes initial therapy patients with active pulmonary tuberculosis to one of four regimens: INH-EMB, INH-RFP, RFP-EMB, and INH-RFP-EMB. To date more than 300 patients have been randomized. When completed in a few years, this well-controlled, carefully designed study should provide definitive answers to various questions about rifampin.

Present evidence suggests that rifampin is an effective, virtually non-toxic antituberculosis drug, which may be useful in the retreatment of patients with tuberculosis, but it is not indicated for initial therapy.

Grateful acknowledgment is made to Dow Chemical Company for supplies of rifampin used in this study.

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TREATMENT OF THE OBESE LATENT DIABETIC

Obesity is closely associated with latent diabetes as well as diabetes. About seven out of eight diabetics when discovered are overweight. By inference then many overweight people must have latent diabetes. . . . To document this condition, the first thing to do is run an oral glucose tolerance test. You'll find it to be slightly elevated in the obese patient, but at the same time you'll find the insulin levels to be inordinately high. . . .

The question comes up "How would you treat this latent diabetes?" You treat it first by weight reduction which, as all of you know, is almost impossible to achieve over a long period of time. In the literature, it's cited that 5 percent of weight reduction is permanently successful and no more.

If that doesn't work, what do you use to improve carbohydrate tolerance? The logical thing is phenformin (DBI) rather than the sulfonylureas because you already have a lot of insulin. What you want to do is facilitate the utilization of glucose which you can do almost independently of insulin with DBI whereas the sulfonylureas push out more insulin. So you give DBI. You find the insulin levels definitely do go down, and yet the carbohydrate utilization improves. So on theoretical grounds, DBI is the method of choice for oral therapy in obese patients. This does not mean that if you use sulfonylureas you can't regularize the blood sugar levels and at the same time achieve a weight reduction, but theoretically DBI is better.

—PETER H. FORSHAM, M.D., San Francisco

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Metronidazole Versus Anaerobes

In Vitro Data and Initial Clinical Observations

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SYDNEY M. FINEGOLD, M.D., *Los Angeles*

■ *Metronidazole, a systemic trichomonicide which has been used extensively since 1960, has recently been shown to be active against various anaerobic bacteria* in vitro *and in experimental infections. In the present study, metronidazole showed significant activity against virtually all of 54 strains of anaerobic and microaerophilic bacteria tested, including Bacteroides fragilis. Since this organism is the anaerobe most commonly isolated from human infections and has demonstrated significant resistance to many antimicrobial agents, metronidazole may prove to be very useful. Our initial clinical evaluation of metronidazole in human anaerobic infections is presented. Because of metronidazole's* in vitro *activity, its low incidence of toxic reactions, and this initial favorable clinical trial, the drug deserves further evaluation in the management of anaerobic infections.*

METRONIDAZOLE (FLAGYL®) was first introduced for the treatment of infections caused by Trichomonas vaginalis in 1959.[1] Subsequently, Shinn reported that metronidazole was effective in the treatment of Vincent's gingivitis.[2] It is also effective in the treatment of tropical ulcer and has been used in primary and secondary syphilis.[3-5] Powell reported the effectiveness of metronidazole in amoebic dysentery and amoebic liver abscess.[6] The first report of *in vitro* susceptibility of an anaerobic bacterium, Bacteroides necrophorus NCTC 7155, to metronidazole was published in 1964.[7] Several recent reports show that metronidazole is active against many different anaerobic bacteria *in vitro* and that it is effective in experimental anaerobic infections.[8-13]

This report presents (1) additional data on *in vitro* effect of metronidazole against various anaerobic and microaerophilic bacteria, including 13 strains of B. fragilis (previously only one strain had been studied) and several other species not previously tested, and (2) our initial clinical experience with metronidazole in treatment of deep-seated anaerobic infections.

Patients and Methods

Methods

The susceptibility of 54 strains of anaerobic or microaerophilic bacteria to metronidazole was determined by agar dilution technique. The inoculum consisted of a 48-hour culture in fluid thiogly-

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collate medium (BBL) enriched with 25 percent ascitic fluid, diluted to approximately 10^5 to 10^6 organisms per milliliter. This was applied to the blood agar (BBL infusion agar base) plates containing various concentrations of metronidazole by means of a replicating device. The tests were incubated for five days and the minimal inhibitory concentration (MIC) recorded as the highest dilution on which no growth occurred.

Patients

Patients with anaerobic infections who were able to take oral medication were selected for clinical evaluation of metronidazole. The drug was administered in a dose of 250 mg by mouth every eight hours.

Case Reports

First Case

A 25-year-old Mexican-American man was admitted with a two-week history of fever following a brief episode of pharyngitis. He had been treated with ampicillin 250 mg every 6 hours before entering the hospital. On the third hospital day his temperature was 40.6°C (105°F) and the only physical finding was slight liver tenderness to percussion. Leukocytes numbered 20,900 per cu mm. On the fifth hospital day, blood cultures were positive for a pleomorphic Gram-negative rod, later identified as Fusobacterium necrophorum (Sphaerophorus necrophorus). The patient was started on metronidazole and became afebrile in 24 hours. Blood cultures became sterile. (See Chart 1). The minimum inhibitory concentration (MIC) of metronidazole for the identified organism was ≦ 0.1 mcg per ml. The patient was treated for 23 days and at last report had remained symptom-free for two months following therapy.

His hospital course was complicated by nonoliguric renal failure, abnormal liver function tests and moderate anemia. These were evident before treatment was begun and returned to normal during therapy. Extensive evaluation during the stay in hospital failed to reveal a portal of entry for sepsis. Liver scans were negative.

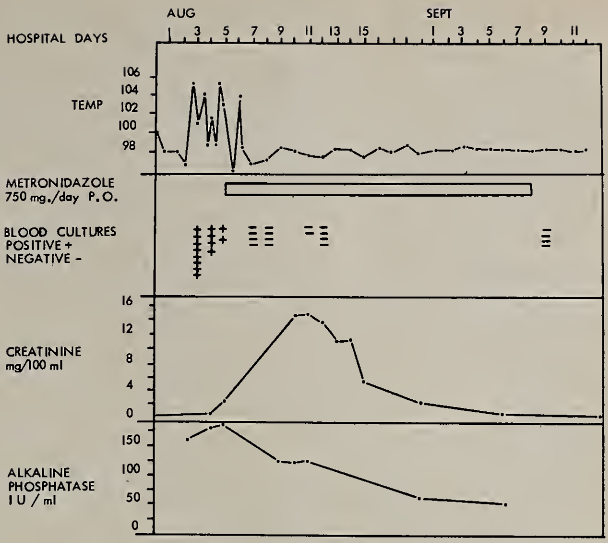

Chart 1.—Clinical Course, First Case.

Second Case

A 66-year-old man, an alcoholic who also used barbiturates excessively, was admitted with fever, cough productive of foul-smelling purulent sputum, a 30-pound loss in weight and a history of several periods of unconsciousness. On examination he appeared chronically ill and lethargic, and there were diffuse rales and rhonchi throughout the left lung. A chest x-ray film showed a diffuse infiltrate in the posterior segment of the left upper lobe and the superior segment of the left lower lobe. Gram stain of the sputum revealed numerous pleomorphic organisms and the patient was started on chloramphenicol for suspected aspiration pneumonia. He was subsequently switched to erythromycin when severe diarrhea developed.

Because the fever and productive cough persisted and an x-ray film showed progression to necrotizing pneumonia despite ten days of erythromycin therapy, percutaneous transtracheal aspiration (TTA) was performed. The purulent, fetid sputum obtained showed pleomorphic Gram-negative and Gram-positive bacilli on stain. Culture yielded Eubacterium lentum and an unidentified non-sporulating Gram-positive anaerobic bacillus.

The patient was started on metronidazole, and there was gradual defervescence and decrease in cough over the first several days. He was treated for a total of 42 days, the pulmonary infiltrates gradually resolving. The hospital course was complicated by normochromic normocytic anemia and a urinary tract infection with Pseudomonas which was treated with a seven-day course of gentamicin. At last report he was afebrile and without cough, two months after com-

TABLE 1.—*Susceptibility of Anaerobic and Microaerophilic Bacteria to Metronidazole*

Organism	*Number of Strains*	*Minimum Inhibitory Concentration (µg/ml)*									
		≦ 0.1	*0.2*	*0.4*	*0.8*	*1.6*	*3.1*	*6.2*	*12.5*	*25*	*>100*
Bacteroides fragilis	13			2	4	2	4			1	
B. melaninogenicus	3			1	1	1					
B. oralis	3				1			1	1		
B. corrodens	4				1	1	1	1			
Fusobacterium nucleatum	5	5									
F. necrophorum	1		1								
F. varium	6			6							
F. species	1					1					
Bifidobacterium	4					1		3			
Clostridium sp.	5	1	1		1		2				
Microaerophilic Gram-pos. cocci	6			2	1	2					1
Veillonella	3					2	1				
Total	54										

pletion of therapy, but had decreased pulmonary function with residual scars and pleural thickening observed on x-ray films of the chest.

Third Case

A 53-year-old diabetic man was admitted with a one-month history of dull pain in the left side of the chest, cough productive of "bad tasting" sputum, and low grade fever.

He had been in hospital in October 1970 with a left lower lobe (superior segment) infiltrate, and while he was being evaluated there, focal seizures developed. He proved to have a brain abscess from which Fusobacterium nucleatum was isolated in pure culture. Gram stain of a TTA specimen after the start of therapy showed a similar organism but failed to yield any growth. He was treated initially with chloramphenicol and then with lincomycin for six months. He was left with a residual focal seizure disorder.

On physical examination at the present admission, poor dental hygiene and localized rales in the left upper lobe were noted. Chest x-ray films showed a posterior left upper lobe infiltrate, and dental films revealed periapical abscesses. Gram stain of the TTA specimen revealed slender Gram-negative filamentous rods and culture of the specimen grew Fusobacterium nucleatum in pure culture.

The patient was treated with metronidazole for 90 days with initial prompt defervescence and slow resolution of the pulmonary infiltrate. All remaining teeth were extracted. The hospital course was uncomplicated. When last seen, six weeks following cessation of metronidazole therapy, the patient was asymptomatic and chest x-ray films show only a residual scar.

Results

The MIC's of the 54 strains of anaerobic bacteria are shown in Table 1. Fifty-one strains were sensitive to metronidazole in concentrations of 6.2 µg per ml or less. One microaerophilic coccus strain grew in the presence of 100 µg per ml of metronidazole.

The three anaerobic infections treated with metronidazole were cured. No adverse reactions to metronidazole were noted. In Cases 1 and 2 mild anemia developed during the illness but in both cases the hematocrits were rising while metronidazole was being administered.

Discussion

The importance of anaerobic bacteria in human infections is being recognized increasingly. While most of these organisms are susceptible to several commonly used antimicrobial agents, Bacteroides fragilis (the most commonly encountered anaerobe) is resistant to penicillin and has developed significant resistance to tetracycline in the past few years.[14] Chloramphenicol is the only antibiotic approved in the United States for

TABLE 2.—*Summary of* In Vitro *Data in the Literature on the Susceptibility of Different Strains of Anaerobic Bacteria to Metronidazole*

Organism	References	Range Sensitive (≦6.2 mcg/ml)	 Intermediate (>6.2 mcg/ml to <50 mcg/ml)	 Resistant (≧50 mcg/ml)
Clostridium perfringens	8,10,13,19	20*	3	3
Clostridium species	8,10,11,13,18	55	4	0
Fusobacterium species	10,11,18	20	0	0
Sphaerophorus species	7,11,12,13	30	2	0
Bacteroides species	10,11,13	24	3	0
Peptococcus	11,13	11	1	1
Peptostreptococcus	11,13	1	1	7†
Veillonella	9,11,13,18	35	3	1

*Number of strains

†Dr. Ueno (personal communication) indicates that all of these strains became facultative on subculture. They always grew better under anaerobic conditions, although they would grow aerobically. All belong to the species P. evolutus, whereas the strain of Peptostreptococcus with intermediate sensitivity was P. anaerobius.

anaerobic infections which is consistently active against B. fragilis. Clindamycin* shows good activity against almost all anaerobic bacteria *in vitro*, and initial clinical trials are encouraging.[15] These latter two agents are bacteriostatic against B. fragilis. Felner and Dowell,[16] in their discussion of anaerobic endocarditis, pointed out the need for a bactericidal antibiotic against B. fragilis. Our laboratory has been testing several agents *in vitro* which show activity against anaerobes. Metronidazole was unique in showing very good bactericidal activity against 19 strains of B. fragilis tested.[17] The broad activity of metronidazole against anaerobic bacteria is reflected in our results. The *in vitro* data from the literature on the activity of metronidazole against various anaerobic bacteria is summarized in Table 2.

As was noted in the introduction, the list of microorganisms which are susceptible to metronidazole has been expanding over the past 12 years. The common characteristic of these various organisms is that they are all anaerobic, as was pointed out by Prince et al.[18] A large number of strains of many aerobic bacteria and several strains of fungi have been shown to be resistant to metronidazole.[10,18,19] Metronidazole has recently been shown to inhibit electron transport systems in T. vaginalis, which probably explains its selective activity against anaerobic organisms.[20] (This may be why certain microaerophilic bacteria are resistant to metronidazole; some of these organisms are undoubtedly facultative rather than anaerobic).

Metronidazole (1- [2-hydroxyethyl] -2-methyl-5-nitroimidazole) is available only in oral form. Peak serum levels following a single 200 mg oral dose range from 2.6 to 7.0 mcg per ml, and following 200 mg three times a day the range is from 6.1 to 9.8 mcg per ml.[21] With doses of 1 gram four times a day, serum levels range from 15 to 72.5 mcg per ml.[3] The drug is 20 percent bound to plasma proteins, which has little effect on its pharmacokinetics.[22] It is partially metabolized in the liver; the major metabolite results from oxidation of the 2-methyl radical.[23] Approximately 60 to 70 percent is excreted in the urine unchanged.[24] Metronidazole is excreted primarily in the urine, both in active form and as inactive metabolites. The biliary tract is not a major route of excretion, although therapeutic levels may be achieved in bile. Because of metronidazole's excellent absorption and almost total excretion via the urinary tract, only very small amounts reach the large intestine.[25] Preliminary data on one patient currently being treated shows negligible changes in fecal flora as compared with a pre-treatment specimen. If it can be verified that normal bowel flora is not greatly altered by the drug, that would represent a distinct advantage over other drugs such as clindamycin. Metronidazole is known to be taken up rapidly by all tissues in experimental animals and to cross the placental barrier in mice.[13,25] In man, significant levels have been demonstrated in pus from a liver abscess, in breast milk and in cerebrospinal fluid.[3,26,27]

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*Clindamycin has recently been approved by the FDA for use in anaerobic infections.

Adverse reactions to metronidazole, which have been infrequent, include gastrointestinal disturbance (vomiting, diarrhea and cramping), metallic taste, urticaria, vaginal and urethral burning and, rarely, darkening of the urine.[28] Metronidazole has been shown to cause a transient neutropenia[29] which is promptly reversible on discontinuation of treatment. Ataxia, vertigo and headache have occurred in humans. A high incidence of psychotic reactions developed in alcoholic patients treated with metronidazole combined with disulfiram.[30] The safety of metronidazole in pregnancy has not been adequately tested. Alcohol is contraindicated while patients are receiving metronidazole therapy.

The *in vitro* evidence of impressive activity of metronidazole against anaerobic bacteria and the good response of our patients indicate that this drug may have a significant role in the treatment of anaerobic infections. The bactericidal activity of metronidazole would make it especially useful in anaerobic endocarditis. Further clinical evaluation of this drug in anaerobic infections of all types is indicated. However, it must be remembered that metronidazole is still experimental for this purpose. Patients should be fully informed and careful pre-treatment and followup bacteriologic studies should be performed.

Addendum

Since preparation of this report, two additional patients with anaerobic infection have been started on metronidazole therapy and are currently still under treatment. One has a necrotizing pneumonia; four anaerobic organisms were recovered from a TTA specimen. One of the four is Bacteroides melaninogenicus, one is probably Fusobacterium nucleatum, one is probably B. fragilis, and one is still unidentified. This patient has been receiving treatment for six weeks. He has shown slow but consistent improvement; there is no longer roentgenographic evidence of excavation, but some infiltrate persists. The second patient has an asymptomatic lung abscess with an anaerobic Gram-negative bacillus (probably a Fusobacterium) recovered in pure culture from a TTA specimen. There has been no change in the size of the abscess cavity after five weeks of metronidazole therapy. Workup for malignant disease, tuberculosis and fungus infection is negative to date.

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Current Concepts in the Management of Carcinoma of the Prostate Gland

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CARCINOMA OF THE PROSTATE gland leads all male cancer in incidence and prevalence and is the second leading cause of death due to cancer in men.[1] Epidemiologic studies[2] show that the highest incidence and death rates for this neoplasm occur in Negroes who reside in the United States, although the incidence and death rate among African Negroes is low. The lowest incidence and death rate occur among native Japanese, but both the incidence and death rate of this neoplasm are fairly high for Japanese who have come to the United States. These observations raise a still unanswered question regarding the influence of environment upon this tumor.

Radical perineal prostatectomy was first advocated by Young[3] in 1904 as a possible curative procedure for this disease. Later, in 1941, Huggins and Hodges[4] published their original work that demonstrated hormonal dependence of this neoplasm and indicated a role for orchiectomy and estrogen therapy in the management of patients with prostatic carcinoma. Subsequently, for several years a rather stereotyped philosophy of therapy for prostatic carcinoma evolved: (1) radical prostatectomy if the tumor was clinically confined to the gland, and (2) castration or estrogen therapy or both if there was extraprostatic extension. Within the past decade new information has evolved which challenges such stereotyped treatment: (1) the advent of lymphangiography and the use of lymphadenectomy or lymph node biopsy for surgical staging of disease has demonstrated early metastasis to lymph nodes, even before bony metastasis; (2) demonstration by the Veterans Administration Cooperative Urological Research Group[5-8] that standard therapy with 5.0 mg per day of diethylstilbestrol is associated with increased mortality from cardiovascular disease as compared with patients who receive a placebo; and (3) growing evidence of an important role of supervoltage external irradiation as a mode of primary therapy.

In view of this new information, it seems timely to review the current status of management of this common cancer.

Latent Carcinoma

Latent or occult carcinoma of the prostate exists when histologic evidence of carcinoma is present within the confines of the prostatic capsule but the patient has no symptoms referable to the lesion, no evidence of carcinoma by rectal palpation, and no laboratory evidence of the disease. This condition is usually discovered as an incidental finding in patients who have undergone transurethral or enucleative prostatectomy for benign hyperplasia or as an incidental finding at autopsy of patients who have died of unrelated disease.

In 1971 Wydner et al[2] compiled a table of the relative incidence of latent carcinoma of the prostate. This table includes one or more autopsy series each from the United States, Canada, England, Austria, and Japan. Table 1 is a modified version of that table. Although the incidence of clinical carcinoma is quite low in Japan, the incidence of latent carcinoma is similar to that reported by other countries.[2] From these data it is apparent that the incidence of latent prostatic carcinoma tends to rise with increasing age of the male population. Denton and associates[9] studied a group of men (all over the age of 50

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TABLE 1.—*Incidence of Latent Carcinoma of the Prostate Gland*

Age Group	*No. men with latent carcinoma per autopsy**	*Percent*
50-59	64/717	9
60-69	145/808	18
70-79	172/596	30
80+	49/190	26

*Composite autopsy studies from U.S.A., Canada, England, Austria, and Japan. Data modified from Wydner EL, et al[2]

years) who had transurethral resection of the prostate for benign hyperplasia. By using the step-section technique rather than routine processing of tissue, they found a 21 percent incidence of occult carcinoma. From their study it was estimated that routine processing of such tissue picks up only 28 percent of the occult carcinomas that can be identified by step-section of all tissue removed.

What is not known is (1) how many men who have latent carcinoma will eventually develop clinical carcinoma of the prostate, or (2) what is the lag period between latent carcinoma and clinical carcinoma of the prostate. Should a man who has a small focus of carcinoma in the specimen of a transurethral or enucleative prostatectomy done for benign hyperplasia receive additional therapy? Some clinicians[10-15] choose to follow such patients conservatively with periodic rectal examinations and recommend specific therapy only if palpable evidence of a "growing" lesion develops. Others[16-19] prefer to proceed with radical prostatectomy. Some such patients are currently being referred for radiotherapy to the residual prostatic tissue. Although several studies seem to justify a conservative approach to latent carcinoma, Munsie and Foster[20] carefully followed 20 patients who had small foci of latent carcinoma in their transurethral resection specimens. In comparing this group with a control group of 33 men who had clinically apparent, but localized, carcinoma of the prostate (Table 2), these investigators noted no significant difference in the age at the time of diagnosis, the five-year survival rate, the average length of survival, or the rate of local recurrence. Sizable amounts of clinical carcinoma eventually developed in about 50 percent of cases, and metastasis developed in two cases. A greater percentage of patients in the control group did die of carcinoma.

TABLE 2.—*Course of Patients with Latent Carcinoma Versus Patients with Localized Prostatic Cancer**

	Latent Carcinoma	*Overt But Localized Carcinoma*
Number of Patients	20	33
Mean Age at Diagnosis	72.9	71.9
Hormone Therapy	60%	94%
Mean Survival After Diagnosis (Months)	62	63
5-year Survival	9 (45%)	17 (52%)
Developed Metastases	2 (10%)	10 (30%)
Died from Carcinoma	2 (10%)	15 (45%)
Well Differentiated	12 (60%)	4 (8%)

*Modified from Munsie WJ, Foster EA[20]

Clinical Carcinoma

In its earliest stage carcinoma of the prostate produces no symptoms. Annual rectal examination is important because the palpatory finding of a suspicious nodule remains the only way for a physician to discover prostatic carcinoma in its early stage. The early malignant nodule is frequently located in the posterior lobe of the gland, and, thus, is readily accessible to the examining finger in the rectum. McNeal[21] and others[22-24] have clearly shown, however, that prostatic cancer often arises in areas other than the posterior lobe. Characteristically, the early malignant nodule is flat and stony hard. More advanced carcinoma may involve an entire lobe or both lobes; late findings include extraprostatic extension, as evidenced by lateral fixation of the gland or extension into the seminal vesicles.

Since benign lesions can exactly simulate the palpatory findings of early carcinoma of the prostate, biopsy is the only way the correct diagnosis can be established. Indeed, at the Johns Hopkins Hospital,[1] of 211 hard nodules (thought clinically to represent malignant disease) that were subjected to open perineal biopsy, only 103 (49 percent) were actually found to be cancer. Other causes of "hard" prostatic nodules include (1) spheroids of benign prostatic hyperplasia, (2) localized inflammatory changes with fibrosis, (3) small prostatic infarcts, (4) prostatic calculi, and (5) granulomatous prostatitis.

Clinical Classification

Various classifications of carcinoma of the prostate according to clinical stage are used at different centers, a fact which causes confusion when one attempts to compare results in various

TABLE 3.—*Classification of Prostatic Cancer*

Stage I:	Tumor confined to prostate gland, not detectable by rectal examination.
Stage II:	Tumor confined to prostate gland, but detectable by rectal examination.
Stage III:	Locally extended tumors.
Stage IV:	Tumors with evidence of distant metastasis obtained by biopsy, radiography, detection of acid phosphatase elevations.
Stage A:	Occult tumor with microscopic foci found incidental to resection for a benign condition or at autopsy.
Stage B:	Disease confined within the capsule, no acid phosphatase elevation.
Stage C:	Extracapsular cancer, regardless of acid phosphatase level, or intracapsular disease with enzyme elevation.
Stage D:	Demonstrable involvement beyond the pelvis or demonstrable metastasis.

TABLE 4.—*Fifteen-year Results of Stage II (Stage B) Prostatic Cancer Treated Only by Radical Prostatectomy at the Johns Hopkins Hospital**

	Number	*Lived 15 Yr With Or Without Cancer*	*Lived 15 Yr Without Evidence of Cancer*	*Died Within 15 Yr With Cancer*
Total Cases	103	36 (35%)	28 (27%)	24 (23%)
Localized Cancer	86	35 (41%)	28 (33%)	14 (16%)

*Table modified from Jewett HJ[27]

published series. Many employ a roman numeral classification, while others prefer the alphabetical staging classification. Two common classifications are described in Table 3.

As to prognosis, even more important than clinical stage is the histologic grade of the tumor. In general, almost regardless of stage, the more undifferentiated the tumor is histologically, the worse is the prognosis, regardless of the treatment employed.[14, 25-28]

Modes of Treatment

Classically, the preferred treatment for Stage II (Stage B) prostatic carcinoma in men who are otherwise fairly healthy and have a life expectancy of 10 or more years has been radical prostatectomy by either the perineal or retropubic route. This operation entails total removal of the prostate gland and the seminal vesicles, but does not include regional lymph nodes. The major morbidity from this procedure has been partial to complete postoperative urinary incontinence in about 20 percent of patients[27-28] and postoperative sexual impotence in at least 90 percent.[27] In two large series of radical prostatectomy[26-31] histologic examination of the surgical specimen revealed significantly more extensive tumor than had been appreciated clinically in about 50 percent of cases; in other words, about 50 percent of the cases had been understaged preoperatively.

To properly evaluate the results of a given form of therapy, one must be aware of the often indulant nature of prostatic carcinoma. Patients may survive for long periods even without treatment, particularly in cases of low grade neoplasms. Indeed, in 1967 Cook[29] reported that six of twenty-five patients (24 percent) lived for ten years without treatment. In a larger group of patients who received only transurethral resection for prostatic carcinoma between 1934-1942 at the Mayo Clinic,[25] 67 of 195 (34 percent) survived five years, 31 of 195 (16 percent) survived for ten years, and 12 of 195 (6 percent survived 15 years. Therefore, to judge the true influence of a given form of therapy upon survival, one needs to know the 15-year survival of patients who received that therapy as the only form of treatment. Several large series of 10-year and 15-year follow-up of radical prostatectomy[26,28-31] must be viewed cautiously because, in addition to radical operation many patients also had postoperative castration or treatment with estrogen.

Perhaps the best longterm series of patients treated solely by radical prostatectomy is that reported from the Johns Hopkins Hospital by Jewett. [27] Before January 1, 1951, 111 patients had radical perineal prostatectomy for Stage II (Stage B) carcinoma of the prostate gland. Eight patients were lost to follow-up, leaving 103 with complete records available for a 15-year follow-up study. The results of this study are shown in Table 4. Only those patients with grade 1 and grade 2 carcinomas survived; all patients with high grade neoplasms were dead within 15 years. Seventeen patients had microscopic evidence of extension of tumor beyond the prostatic capsule; only one of these patients survived for 15 years. Thus, the 15-year survival of men (average age at operation 61.9 years) who had radical perineal prostatectomy for clinical Stage II (Stage B) carcinoma was 35 percent, 8 percent of whom still had evidence of cancer. Of those whose cancer was histologically confined within the prostatic capsule, 33 percent were alive without evidence of cancer 15 years later.

This series of radical prostatectomy for Stage II (Stage B) carcinoma of the prostate should be compared with a smaller, but comparable, series of patients with Stage II carcinoma treated solely by castration or estrogen and reported by Barnes.[32] Sixteen of 74 patients (22 percent) lived 15 years without evidence of cancer and 24/74 (32 percent) died of cancer or were lost to follow-up. Thus, the 15-year survival without evidence of cancer was better in the surgical group, but only by 11 percent.

Before 1956 the use of radiotherapy as a primary form of treatment for prostatic carcinoma was rare.[33] During the past decade supervoltage external irradiation has been used increasingly as an alternate to radical operation or palliative endocrine manipulation. Perhaps the largest group of patients who have been followed for the longest time after primary irradiation of the prostate gland is the series from Stanford.[34] From September 1956 through December 1969 310 patients with localized disease and no apparent metastasis received irradiation via the linear accelerator at Stanford University. The area treated included the prostate gland, the surrounding soft tissues, the seminal vesicles, the bladder neck, and the immediately adjacent lymph nodes. Therapy was designed to deliver a maximum of 7,500 rads to the center of the gland and a minimum of 3,500 rads to the lateral pelvic sidewalls over a course of some seven weeks. Among the patients treated, 160 had disease limited to the prostate (DLP), or Stage II carcinoma, and 150 had extracapsular extension (ECE), or Stage III (Stage C) carcinoma. In the DLP group, 130 patients were said to have had neoplasia involving more than 50 percent of the gland, while only ten patients (6 percent) had a small nodule involving 25 percent or less of a single lobe. Table 5 shows the actual five-year results, and Table 6 shows the actual ten-year results of radiotherapy as the only therapeutic modality for Stage II, and Stage III carcinoma. These results should be compared with those in a similar group of patients who had radical perineal prostatectomy at the Johns Hopkins Hospital[27] (Table 7).

TABLE 5.—*Five-year Success Rate of Radiotherapy for Prostatic Carcinoma (Stanford University)**

Clinical Stage	*Patients At Risk*	*Alive With Or Without Cancer*	*Alive Without Cancer*	*Dead From Cancer*
DLP (Stage II)	53	37 (70%)	35 (66%)	8 (15%)
ECE (Stage III)	34	17 (50%)	14 (41%)	12 (35%)

DLP—Disease limited to prostate; ECE—Extracapsular extension

*Data modified from Ray GR, et al[34]

TABLE 6.—*Ten-year Success Rate of Radiotherapy for Prostatic Carcinoma (Stanford University)**

Clinical Stage	*Patients At Risk*	*Alive With Or Without Cancer*	*Alive Without Cancer*	*Dead From Cancer*
DLP (Stage II)	18	11 (61%)	10 (56%)	2 (11%)
ECE (Stage III)	5	2 (40%)	1 (20%)	2 (40%)

*Data modified from Ray GR, et al[34]

TABLE 7.—*Ten-year Success Rate of Radical Prostatectomy for Prostatic Carcinoma (Johns Hopkins Hospital)**

			Alive Without Cancer			
Clinical Stage	*No. of Patients*		*No. of Patients*		*Percent*	
Discrete Nodule (Stage II)	103	182	52	81	50	44.5
Larger But Confined To Prostate (Stage II)	79		29		37	
Extraprostatic (Stage III)	48		0		0	

*Modified from Jewett HJ, et al[27]

Although the number of patients who have actually been followed for 10 years post-irradiation is quite small, from these data one can see that the overall survival (without evidence of cancer) of Stage II patients treated with radical prostatectomy (44.5 percent) is similar to the survival (without evidence of cancer) of Stage II patients who received irradiation (56 percent). Among the Stage III patients, none survived radical operation at ten years, while one of five patients (20 percent) who received radiotherapy was alive ten years later without known cancer. These figures suggest a definite role for irradiation therapy as a primary form of treatment, although the figures are admittedly small.

Although a significant number of patients experience irritative voiding symptoms and some degree of temporary diarrhea in conjunction with radiotherapy, only about 10 percent have persistent, severe voiding or rectal symptoms. Following irradiation up to 30 percent of patients have noted sexual impotence, which compares favorably with the 90 to 100 percent incidence of impotence that follows radical prostatectomy. Although the early results of radiotherapy as a primary form of treatment for prostatic carcinoma are encouraging, experience with 10-year and 15-year results in a large number of patients is still lacking.

For many years the disposition of prostatic carcinoma to metastasize early to bone, particularly to the lumbar vertebrae and bony pelvis, has been appreciated. This has been attributed to the relationship of the prostatic venous plexus to the vertebral venous plexus. Although autopsy studies in the past have clearly shown metastasis to the pelvic and para-aortic lymph nodes, the realization that early metastasis to pelvic lymph nodes, even before detection of osseous metastasis, has come only in recent years with the advent of pelvic lymphadenectomy in cases of carcinoma of the prostate. In 1959, Flocks and associates[35] reported their eight-year experience with pelvic lymphadenectomy in 411 patients with Stage II and Stage III prostatic carcinoma. Of 29 patients with Stage II carcinoma, two (7 percent) had positive lymph nodes. In patients who had Stage III carcinoma, the occurrence of regional lymph node metastasis relative to the estimated weight of the prostatic lesion was as follows: (1) with the prostatic tumor under 35 grams, 24 of 130 patients (18 percent) had metastasis; (2) with the prostatic tumor from 35 to 80 grams, 81 of 185 patients (44 percent) had metastasis; (3) with the prostatic tumor from 80 to 150 grams, 28 of 55 patients (51 percent) had metastasis; (4) with the prostatic tumor larger than 150 grams, 11 of 12 patients (92 percent) had metastasis. Arduino and Glucksman[36] performed complete pelvic lymphadenectomy at the time of radical retropubic prostatectomy for Stage II prostatic carcinoma in 44 patients and found 14 patients (32 percent) with lymph node metastasis. Ten of 11 patients (91 percent) who had histologic evidence of involvement of the seminal vesicles had positive regional lymph nodes.

Obviously, when disease has already spread to regional lymph nodes, neither radical prostatectomy nor prostatic irradiation is adequate for cure. Whether the addition of pelvic lymphadenectomy or irradiation with a wide field to include all pelvic lymph nodes will improve survival is at present highly speculative. Because of the potential of increased morbidity associated with extending the field of irradiation to include pelvic, and perhaps para-aortic lymph nodes, such therapy should probably be limited to patients having biopsyproved nodal involvement. The current policy at Stanford University is to perform lymphangiograms on all patients with Stage II and Stage III prostatic carcinoma. Unless specifically contraindicated, exploratory laparotomy is then performed for surgical staging. Any suspicious or positive nodes noted on the lymphangiogram are excised, along with representative para-aortic and bilateral common iliac, external and internal iliac lymph nodes. In addition to postoperative irradiation to the prostate, those patients who have positive lymph nodes receive 5,000 to 5,500 rads to the upper limits of nodal involvement.

The role of endocrine therapy for carcinoma of the prostate remains highly controversial. In a study of a large group of patients by Nesbit and Baum,[37] the five-year survival of patients presumably with Stage III prostatic carcinoma treated by endocrine therapy alone were as follows: estrogen only, 29 percent; orchiectomy only, 31.2 percent; orchiectomy plus estrogen, 43.6 percent. The five-year survival of a group of patients who were untreated was only 10 percent. In a study from the Mayo Clinic, Emmett and associates[38] reported survival among patients treated with endocrine therapy for Stage III (some cases of Stage II carcinoma may have also been included) as follows: early castration (about 50 percent also received estrogen), five-year survival of 56.8 percent, 10-year survival of 26.5 percent; early estrogen, five-year survival of 35.4 percent, ten-year survival of 11.5 percent. In a group of similar patients who received no therapy other than transurethral resection, the five-year survival was 15.4 percent, the ten-year survival 5.1 percent.

These two studies of a large group of patients with Stage III prostatic carcinoma suggest that (1) the survival of patients who received castration alone, or estrogen alone, is greater than that of untreated patients; (2) the survival of patients treated with estrogen alone is about the same as that of patients treated with castration alone; and (3) the survival is enhanced when castration and estrogen are combined.

In sharp disagreement with these earlier conclusions regarding the role of endocrine therapy in prostatic cancer have been the results of the Veterans Administration Cooperative Urological Research Group.[5-8] In the original study patients with Stage III carcinoma were randomized into four groups: (1) placebo only, (2) orchiectomy plus placebo, (3) estrogen only, and (4) orchiectomy plus estrogen. In 1967,[5] when the initial results of this study were reported, five-year survival figures were available with approximately 250 patients in each treatment category. Surprisingly, the best survival was in the group that received placebo only (58 percent), while the poorest survival was in the group that received both castration and estrogen (46 percent). In a large series of patients with Stage IV prostatic carcinoma that had similar treatment randomization, the percentage of patients who survived with placebo only was essentially the same as that of patients who received both castration and estrogen. This study indicated no significant enhancement of survival of patients with either Stage III or Stage IV prostatic cancer by endocrine therapy. Furthermore, both this report and a later report by Blackard et al[7] demonstrated a statistically significant increase in mortality due to cardiovascular deaths among patients who received estrogen (all patients received standard dosage of 5.0 mg of diethylstilbestrol daily). Early results of a subsequent study[8] indicate that therapy with 1.0 mg of diethylstilbestol daily equals the 5.0 mg dose in controlling prostatic carcinoma and significantly reduces the incidence of cardiovascular complications associated with the larger dose.

The major conclusions drawn from the Veterans Administration study are that (1) although endocrine therapy often affords considerable palliation (relief of pain and urinary obstruction), it does not prolong the life expectancy for patients who have prostatic carcinoma, (2) endocrine therapy is probably best withheld until obstructive symptoms or bone pain develop, (3) therapy with 5.0 mg per day of diethylstilbestrol causes a significant number of complications and deaths from cardiovascular disease, and (4) since a daily dose of 1.0 mg of diethylstilbestrol equals the 5.0 mg dose in controlling the tumor with significantly fewer cardiovascular complications, little justification remains for the use of a daily dose larger than 1.0 mg of diethylstilbestrol in the treatment of prostatic carcinoma.

Two major criticisms have been made of the Veterans Administration study: (1) a significant number (perhaps up to 25 percent) of patients eventually received some form of therapy other than that of their original randomization, yet all patients were kept in their original randomization categories in the final statistical analysis of the data, and (2) the patients were followed almost exclusively by urologists, who may not have rendered optimal attention to the cardiovascular complications that developed during estrogen therapy.

The precise cause of this increased mortality from cardiovascular disease that is associated with estrogen therapy is not fully understood. Fluid retention may play a role, but a perhaps more important etiologic theory relates to the effect of estrogen upon certain serum proteins. Doe and coworkers[39-41] observed that corticosteroid-binding globulin, 17-hydroxycorticosteroids, ceruloplasmin, beta-glucoronidase, and plasminogen rise predictably when small doses of estrogen are administered. This rise in post-treatment values is dose-related; hence, the larger the dose of estrogen, the greater is the rise in these serum proteins. Plasminogen activation usually declines in the aging male, and estrogen reportedly suppresses plasminogen activation. Conversion of plasminogen to plasmin is likely necessary in the maintenance of the patency of blood vessels by its prevention of fibrin deposition on the endothelial lining. Doe and associates have observed that plasminogen levels are greater in estrogen-treated patients than in those who are receiving placebo. This rise in plasminogen level is generally dose-related, and may reflect decreased plasminogen activation.

Without some comments regarding immunologic studies of the prostate, this review would be incomplete. In 1969 Ablin and coworkers[42] summarized their work regarding immunologic aspects of the prostate gland, particularly with regard to cryosurgery. Experimental work with monkeys, dogs, and rabbits have shown that cryosurgical treatment of the prostate gland results in a rapid rise in serum autoantibodies that are species and tissue specific against the animal's own prostatic tissue. Refreezing of the prostate for a second and third time at intervals of 30 days was associated with a temporary rise and fall of circulating autoantibody that was species and tissue specific against prostatic tissue on each occasion.

Case histories of seven patients with metastatic carcinoma of the prostate who underwent single or multiple cryosurgical procedures of the prostate were reviewed. In each case obvious regression to complete remission of both pulmonary and osseous metastatic lesions was noted postoperatively. The cryosurgical procedure theoretically produces circulating autoantibodies that are capable of destroying prostatic tumor cells throughout the body. Repetitive freezing of the prostate is recommended by these investigators as a means of boosting and sustaining the level of these antibodies in the serum. Although much additional work is needed to further elucidate these findings, the early results are exciting. This observation must still be viewed with caution, however, since similar antibodies have been associated with other neoplasms[43-47] with no apparent protective effect against the tumor or its metastases.

Concluding Remarks

If nothing else, this review serves to point out the wide variation in results of various modes of therapy that are used in the management of prostatic carcinoma. Probably no other common neoplasm equals carcinoma of the prostate gland in present day confusion regarding what actually is optimal therapy. In part, this confusion is due to the wide variation from patient to patient in the natural history of the disease; in part, it is due to seemingly conflicting reports and variable conclusions that fill the literature.

Although many questions remain unanswered, a few conclusions seem justified: (1) patients who have clinical carcinoma of the prostate are more likely to survive for ten years with some form of treatment (radical prostatectomy, radiotherapy, endocrine therapy) than if they are left untreated; (2) regardless of the therapy employed, the higher the clinical stage of disease, the worse the prognosis; (3) the more histologically undifferentiated the prostatic neoplasm, the worse the prognosis, regardless of the clinical stage or therapy employed; (4) a daily dose of greater than 1.0 mg of diethylstilbestrol is probably no longer justified in the treatment of prostatic carcinoma.

Some general comments regarding the management of prostatic carcinoma are perhaps in order. When a small focus of well-differentiated carcinoma is incidentally found in the specimen following transurethral or enucleative prostatectomy for benign hyperplasia, the patient should be watched carefully but not treated. If subsequent rectal examination reveals evidence of a "growing" lesion or clinical carcinoma, the patient should be managed as having a Stage II carcinoma. If the patient has a 15 or 20 year life expectancy, or if the focus is histologically a high grade lesion, the management should be as for a Stage II carcinoma.

The patient who has Stage II carcinoma should have a lymphangiogram. Even if the lymphangiogram is negative, an abdominal exploration with biopsy of the para-aortic lymph nodes should be done. If frozen section reveals negative para-aortic nodes, either of two forms of therapy are indicated: (1) radical prostatectomy with pelvic lymphadenectomy, or (2) pelvic lymph node dissection followed by postoperative radiotherapy to the prostate and full pelvis. If the para-aortic lymph nodes are positive, radical prostatectomy with pelvic lymphadenectomy will not be curative and is probably contraindicated. Instead, the abdomen should be closed and the patient receive postoperative irradiation to the prostate, full pelvis, and para-aortic lymph nodes. Endocrine therapy should be withheld unless metastasis develops.

The patient who has Stage III prostatic carcinoma should be treated like the patient who has Stage II carcinoma, except that the indication for radiotherapy is greater than the indication for radical prostatectomy with pelvic lymphadenectomy.

When Stage IV prostatic carcinoma is diagnosed, the patient is not a candidate for exploratory laparotomy, radical prostatectomy, or primary radiotherapy. Instead, endocrine therapy is indicated: either castration or therapy with 1.0 mg of estrogen daily. Combined endocrine therapy may also be indicated. Obstructive symptoms may warrant transurethral resection. Palliative radiotherapy may be indicated for symptomatic bony metastasis. For late symptomatic relief the addition of oral steroids (such as prednisone) or cryohypophysectomy may at times afford palliation.

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A CLUE TO MALLORY-WEISS SYNDROME

The Mallory-Weiss syndrome is fairly common. It's a tear in the mucosa right where the esophagus meets the stomach. It's an esophagogastric-mucosal tear. It should be diagnosed if we'd just talk to the patient.

The patient who has a bleeding ulcer or bleeding varix vomits blood. But a patient with a Mallory-Weiss syndrome will tell you, "I retched and I retched and I retched, and finally blood came up." Emesis, emesis, emesis — that's a Mallory-Weiss syndrome until proved otherwise.

—PHILIP THOREK, M.D., Chicago

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Epidemiologic Treatment in Venereal Disease

A Method to Aid in VD Control

ELLIS N. MITCHELL, M.D., *Greenbrae*

■ *Epidemiologic therapy refers to the treatment of infectious syphilis or gonorrhea contacts without proof of laboratory diagnosis. This method of treatment is considered essential by public health authorities in the management of venereal disease, but has long been neglected in the private sector of medicine. The majority of venereal disease patients are treated by private practitioners, but apathetic attitudes, insufficient training, lack of case reporting, differing and often inadequate treatment schedules, poor follow-up and ignorance about or reluctance to use epi-treatment are all factors in our losing struggle against the current venereal disease epidemic.*

EPI-TREATMENT (EPIDEMIOLOGIC THERAPY) means the treatment of infectious syphilis or gonorrhea contacts without proof of laboratory diagnosis.

In spite of the relative ease of diagnosis by trained physicians and the availability of absolute cures, the number of syphilis and gonorrhea cases continues to soar. Gonorrhea cases have reached epidemic proportions and syphilis is well on its way. Reliable surveys indicate that private physicians report less than one-third of syphilis cases and one-tenth of gonorrhea cases.[1] Public apathy, physician indifference and lack of both federal and state funding are leading contributory factors in this problem. These elements coupled with lack of education of physicians and public regarding the problem constitute the basis for the uncontrolled spread of venereal disease.

There is obviously a great need to attack these diseases with multiple approaches to halt their spread. Many ask, "What can be done?"

Epidemiologic treatment is good medical practice and can significantly contribute to the control of gonorrhea and syphilis. Authorities in VD work recognize epidemiologic treatment as paramount in control efforts.[3,4] As with other communicable disease measures, epidemiologic treatment must be weighed by its effect on community health. Its community value should outweigh the individual. The community benefit of epi-treatment seems obvious—to halt ("stat") any possible spread of venereal disease. For the exposed contact the possible treatment complications can be weighed against the tragedy of becoming an untreated person who is lost to medical supervision.[5] Occult gonorrhea can lead to pelvic inflammatory disease, rectal disease, crippling, or ophthalmia neonatorum. Occult syphilis can lead to optic atrophy, other optic disease,[6] paresis, tabes, cardiovascular syphilis, congenital syphilis or death. (Few physicians realize that chronic syphilis causes nearly 3,000 deaths in the United States each year.)

The indications for epidemiologic treatment include both public health and clinical considerations.[1] Coupled with proper examination, epi-

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treatment should be given to all male and female venereal disease contacts at the initial visit. When this is done, the infection will not develop and disease cannot spread to intimate contacts before signs and symptoms appear in the patient. Vaginal, oral and rectal contacts in particular may be expected to have occult primary lesions or asymptomatic gonorrhea.[3,7] Treatment of syphilis or gonorrhea contacts at the time of the initial examination eliminates any infecting organisms during the incubation period, negating the possibility of further disease transmission to all interim contacts during the days, weeks or months before infection becomes manifest. Early syphilis serology is often negative when the patient is most infectious.

Risk of infection from intimate exposure to an infectious person is high. Venereal disease will develop in 20 to 50 percent of named sex contacts.[2] For this reason, the indication for epidemiologic treatment is far greater than the indication for similar treatment for a physician or nurse who is accidentally punctured by a needle while performing a blood test or the indication for retreatment of a pregnant female. Epi-treatment for sex contacts to venereal disease can also be compared with surgical excision of suspicious premalignant lesions, or with the prophylactic treatment of meningitis or tuberculosis contacts or patients with rheumatic fever.

The degree of promiscuity of some patients is of added significance. During the pre-diagnostic period, promiscuous persons may have as many as 20 contacts.[2] Many such patients awaiting definitive diagnosis are lost from surveillance. Furthermore, epi-treatment minimizes re-infection or "ping-pong" infections.

Most patients exposed to venereal disease readily accept their physician's judgment concerning epi-treatment. The sex contact, fearing disease, frequently is relieved by the suggestion. Many patients also realize that treatment affords safety from spread of infection without interruption of sexual activities.[2]

At the initial visit, the venereal disease contact needs a thorough physical examination, appropriate laboratory tests and epi-treatment. While gonorrheal urethritis in males can be confirmed by a simple smear, difficulty is encountered with genito-urinary infection in women or with rectal gonorrhea.[2] Since symptoms are usually minimal or absent, cultures should be performed.[3] Signs and symptoms of early syphilis can either be absent or easily missed by both physician and patient. Careful examination of oral, rectal and genital orifices needs to be made, including darkfield or fluorescent examination of any lesions in addition to the conventional blood test. Next, epi-treatment is administered.

Epi-treatment consists of administration of the same therapy as for clinical disease. For syphilis contacts, a single injection of 2.4 million units of benzathine penicillin G will maintain the necessary blood level of 0.03 units per milliliter for ten days.[8] For therapy of penicillin-sensitive patients, recommended dosages of appropriate broad spectrum antibiotics are 2 to 4 grams daily for ten days, a total of 20 to 40 grams. Contacts to gonorrhea need a high blood level which is maintained for at least 48 hours. Many workers now administer by injection (at one session) from 2.4 to 4.8 million units of aqueous procaine penicillin G (with or without probenecid). Appropriate alternate antibiotics are usable in lieu of penicillin.[3,8]

It should of course be emphasized that some patients are allergic to penicillin and a history of previous hypersensitivity should be sought. Patients receiving intramuscular penicillin should be observed for any immediate allergic signs or symptoms and the physician must be prepared to deal with this situation.

In a pregnant patient who is allergic to penicillin, erythromycin becomes the treatment of choice, since a tetracycline may cause bone lesions and teeth straining in the newborn.

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—Pediatric Grand Rounds, University of California, San Diego (Specialty Conferences). Calif Med 117:37-44, Dec 1972

Specialty Conference

Allergic Rhinitis

Participants: Louis M. Mendelson, m.d., William L. Nyhan, m.d., ph.d., and Robert N. Hamburger, m.d.

Taken from the weekly Pediatric Grand Rounds held at the University Hospital of San Diego County, University of California, San Diego, School of Medicine, November 9, 1971

Dr. Mendelson:* *Case 1.* The patient was an 8-year-old boy referred to the Allergy Clinic for evaluation of possible nasal allergy. The child was entirely well until about three years of age when, following exposure to freshly cut grass, rhinorrhea, paroxysmal sneezing, and itching of the nose developed. He also complained of watery and itchy eyes. These symptoms then continued and occurred perennially, with somewhat lessened severity in the winter. He was awakened two or three nights a week by sneezing and nasal obstruction. He was always lethargic and irritable, and because of his nasal problems he found it difficult to participate in outdoor activities with other children. He used two handkerchiefs a day. His teacher constantly complained about the noise he made when he breathed and said it disturbed others in class. He was being treated with Actifed®†, which helped control the sneezing but made him sleepy.

The nasal discharge was clear and watery. The patient constantly rubbed his nose (the "allergic salute") and made a clicking noise with his tongue because of an itchy palate. His eyes always had dark circles ("shiners") under them.

As an infant he had eczema, but he had not had this problem for the previous five years. There was no history of asthma and no drug or food intolerance.

His mother had had a life long history of rhinitis and asthma. The father and 17-year-old sibling had no history of allergic disease.

There was a history that grass, house dust, and cats could produce nasal symptoms. Other physical findings in the patient included the presence of facial grimacing, allergic salute, a nasal crease, and allergic shiners. The nasal mucosa was pale and boggy, and there was mild nasal obstruction.

Laboratory data showed numerous eosinophils on nasal smear. There was an elevated serum concentration of gamma E immunoglobulin (IgE). Skin tests for reaction to grass, dust and cat danders were immediately positive.

Case 2. The patient, an 8-year-old boy, was referred to the Allergy Clinic for evaluation of noisy breathing which he had had since birth. He had first sought help for this problem two

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†Generic names of proprietary agents mentioned are listed at the end of this article.

years previously. A diagnosis of allergic rhinitis had been made and Chlortrimeton Syrup® prescribed. Subsequently, he was seen several times for the same problem and each time was treated with Dimetapp® and Actifed®. The use of these medications led to minimal improvement of the noisy breathing. His nasal obstruction and noisy breathing were perennial but worse in the winter. In addition, the breathing became more obstructed when he acquired an upper respiratory infection. He did not sneeze. His nose did not itch, and there was no rhinorrhea. He did not have an allergic salute. His nose became obstructed when subjected to extreme changes in temperature or humidity as when going from outdoors into an air-conditioned environment. He had had only one ear infection in his life and rarely had sore throat. There was no history of eczema, hives, drug sensitivity, or intolerance to foods. He had once been stung by an insect, with no significant reaction. He had no symptoms referable to the eyes, he did not cough or wheeze, his exercise tolerance was excellent and his general health was good.

The mother, father, and two siblings had no allergic disease.

Physical examination revealed no significant amount of tonsillar or posterior pharyngeal lymphoid tissue. No posterior pharyngeal discharge was present. Breathing was not obstructed and the nasal passages were dry. The inferior turbinates, especially on the left, were somewhat enlarged. The color of the mucous membranes was normal.

There were very few eosinophils in a smear of material from the nose. Skin testing for sensitivity to ten common inhalants revealed no significant reactions.

Discussion

Rhinitis is one of the most common problems we deal with in the practice of medicine. This is especially true in pediatrics. One of the most common causes of rhinitis is allergy. According to the latest figures from the National Center for Health Statistics, 31 million Americans have one or more allergic disorders, and of these, approximately 13 million have pure allergic rhinitis.[1] Table 1 lists the prevalence of chronic diseases in children. Allergic disorders lead the list.[2] Approximately $135 million is spent annually on prescription drugs for allergic conditions. There is no telling how much is spent for over-the-counter medication.

TABLE 1.—***Prevalence of Selected Chronic Conditions per 1,000 Children under Age 17, by Sex; United States, July 1966-June 1967***

Condition	*Boys*	*Girls*
Hayfever, asthma and other allergies	106.7	90.2
Respiratory conditions	59.9	51.0
Orthopedic impairments and paralysis	24.8	22.0
Speech, hearing and visual impairments	28.1	16.9
Skin infections and diseases	14.3	15.8
Digestive system conditions	13.2	8.5
Mental and nervous conditions	7.3	6.0

Clinical immunologic reactions can be divided into four categories, using the Gell and Coombs classification.[3] Allergic reactions are classified as Type I reactions. These reactions are characterized by the combination of antigen with an antibody. The antibody is fixed to a target cell, which, in the case of allergic rhinitis, is the mast cell. The interaction of the antigen with the antibody causes the release of a mediator, such as histamine, from the target cell. The mediator in turn acts on the target tissue, which in the case of rhinitis is the group of small blood vessels in the nasal mucosa. In this way the symptoms are produced.

The major source of antibody involved in the allergic reaction is IgE.[4] One of the properties that distinguishes IgE from other antibodies is its ability to fix either to mast cells or to basophils, both of which are rich in histamine.

The exact mechanism of the release of histamine is not known. Work by Stanworth suggests that when the antigen combines with IgE, it causes an activating site on the IgE to be exposed, thus facilitating the attachment of this site to a similar site on the mast cell (Figure 1). This reaction then precipitates the release of histamine.[5]

Much has been learned about the mechanism of the release of histamine by the use of the human leucocyte histamine release technique.[6] In essence, this procedure takes advantage of the fact that basophils which contain histamine also fix IgE. The test is performed by mixing basophils which have IgE fixed to them with an antigen and measuring the amount of histamine released. Using this technique the following

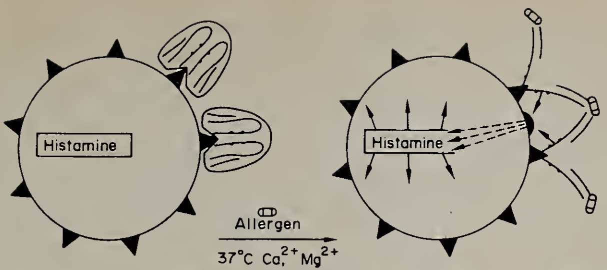

Figure 1.—Postulated manner in which the interaction between cell-bound γ E antibody and allergen triggers the release of vasoactive amines. (Reprinted with permission from Clinical Allergy (1:27, 1971).)

things have been learned: (1) IgE sensitizes basophils. (2) Histamine is preformed in the basophil. (3) The basophil is not destroyed by the histamine release. (4) Complement is not needed for the reaction to take place. (5) Cyclic 3,5-AMP is important in the regulation of the release of histamine.

This neat picture of the Type I reaction does not explain all of the phenomena that we see in clinical allergic rhinitis. For example, a person may inhale large amounts of ragweed pollen in the laboratory out of ragweed season and have no symptoms; yet if he inhales even a small amount during the ragweed season he gets severe symptoms.

To explore this question, John Connell at the Roosevelt Hospital in New York performed what are now considered classic experiments leading to an understanding of allergic rhinitis.[7] With the aid of two instruments which he developed, he was able to produce acute episodes of allergic rhinitis in an individual nostril with a measured number of pollen grains. Concomitantly he measured nasal patency. The latter was an objective measurement of clinical response.

With successive daily nasal challenges out of ragweed season in allergic persons, symptoms began to develop after the second day. By the fifteenth day, one-fortieth the number of pollen grains that caused no symptoms on the first day caused severe nasal obstruction. Connell referred to this as the "priming effect." On day one, 250 pollen grains produced no symptoms; after 15 days of priming 7 pollen grains produced significant obstruction.[8]

Connell next showed that the priming effect was reversible. The time required for reversal depended on the number of days the nostril was primed. After five days of priming, it took three days for the nostril to return to normal, and after five weeks it took four weeks. Similar challenges in non-allergic persons with 5000 times the total dose used in allergic patients produced no obstruction. The priming effect was localized to the nostril primed. As much as 50 times the number of pollen grains that caused severe obstruction on the primed side caused no obstruction on the unprimed side.

Connell's work has also provided an explanation for why people with ragweed-induced allergic rhinitis frequently complain that the only time they have other allergic reactions, for example to cats, is during the ragweed season. He showed that once the nose is primed it will react to any antigen against which the patient has IgE antibodies. At the same time, this was not simply an irritant effect but rather an immunological reaction.[7] A challenge with inert carbon particles of the same size as the pollen grains produced no obstruction.

Nasal biopsy of patients after priming showed fragmentation of the basement membrane. Again, the degree of fragmentation depended on the number of days primed. It is not the number of pollen grains inhaled that causes symptoms but rather the number of antigens that come in contact with IgE. Furthermore, one of the functions of the basement membrane is to keep out foreign antigens. Thus with increased fragmentation of the membrane a greater amount of antigen passes through it and combines with the IgE. Therefore fewer pollen grains need to be inhaled to cause clinical disease.[7]

Clinical Diagnosis of the Disease.

Table 2 lists the three most common causes of rhinitis and the characteristic findings in the history of each. Vasomotor rhinitis refers to chronic rhinitis for which no cause can be found.

Of the cases presented, Case 1 illustrated a classic example of allergic rhinitis. Findings that should make one consider allergy as the cause of rhinitis are the presence of itching in the nose, palate, ears, or eyes (histamine causes itching); paroxysmal sneezing; conjunctivitis; a history of eczema or asthma; a history of attacks of allergic rhinitis precipitated by allergens such as grass, pollen, animal dander, or house dust; seasonal recurrences; or a family history of allergy.

On the other hand, Case 2 was a classic example of vasomotor rhinitis. The patient had

TABLE 2.—*Differential Diagnosis of Rhinitis Historical Aspects*

	Allergic	*Infectious*	*Non-allergic (vasomotor)*
Seasonal incidence	Present seasonally	Absent or worse in winter	Absent or worse in changing season
Recurrences	Mild symptoms present between attacks	Clears completely	Frequently continuous
Family history of allergy	Common	Occasional (coincidental)	Occasional (coincidental)
Constitutional symptoms (sore throat, fever)	Rare	Common	Rare
Other allergic symptoms (asthma, eczema)	Common	Occasional (coincidental)	Occasional (coincidental)
Itching of nose, eyes, palate	Usual	Rare	Unusual
Paroxysmal sneezing	Usual	Rare	Unusual
Allergic salute and nose twitching	Common	Occasional (coincidental)	Occasional (coincidental)
Allergens traced as precipitating factors	Frequent	Unusual	Unusual

This chart is a modification of one in G.M. Sheldon's et al,[17] *a Manual of Clinical Allergy,* W. B. Saunders Co., 1967, Philadelphia.

perennial rhinitis. His nose was very sensitive to changes in weather and temperature. He had none of the allergic symptoms observed in the first patient.

Frequently, the difference between allergic and vasomotor rhinitis is not so clear-cut. The presence of eosinophils in the nasal secretions and elevation of the serum IgE[8] can be helpful in the diagnosis of allergic disease.

Skin testing for immediate reactions is one of the most misused diagnostic tests in medicine. A positive immediate skin test indicates that the patient has skin-fixed antibodies, most likely IgE, to the allergen being tested. It does not necessarily mean that the antigen to which the skin reacts is the cause of the patient's rhinitis. The significance of a positive skin test can only be interpreted in the light of the history. In a patient suspected of having vasomotor rhinitis the absence of positive skin tests can be useful.

Children with perennial rhinitis and a history of frequent formula changes, colic, abdominal pains and leg aches may be allergic to cow's milk.[9] A trial elimination of milk from the diet for a couple of weeks may help. Skin testing for foods offers little help in the diagnosis of rhinitis in children. If a food is suspected the only way to confirm it is by trial elimination and subsequent challenge with the suspected food.

In obtaining the history it is well to devote a good deal of time to obtaining an idea of how the illness affects the child in his daily living. We are interested in how it affects his sleep at night, his play activities during the day, and his school work. In this way we can judge the severity of the patient's problem. It also provides us with markers to help decide whether he is improving or not with treatment.

There are causes of rhinitis other than the three previously mentioned, which are the most common. A more extensive list is shown in Table 3. Two of these causes are especially noteworthy. The first is foreign body. This diagnosis should be considered in all children with chronic rhinitis, whether or not the rhinitis is unilateral and purulent. The other is rhinitis medicamentosa, which results from the overuse of nasal drops or sprays. Many patients use topical vasoconstrictors to alleviate their nasal obstruction, and at first they obtain immediate relief. However, after days of continued use rebound occurs and a vicious cycle is established.

Treatment

The treatment of allergic rhinitis can be divided into the three following categories: (1) avoidance of allergens to prevent allergic symptoms; (2) pharmacological treatment to minimize or counteract the consequences of exposure once it has occurred; and (3) immunological treatment to alter the immunologic response to the allergens.

In avoidance therapy we try to get the patient to avoid, as much as possible, all of the allergens

TABLE 3.—*Diagnosis of Rhinitis*

FOREIGN BODY

ANATOMIC VARIATION
1. Adenoid hypertrophy
2. Choanal occlusion
3. Deviated septum

NEOPLASM
1. Sarcoma
2. Polyps
   - a. Cystic fibrosis
   - b. Allergy
   - c. Aspirin

INJURY
1. Direct trauma
2. Reaction to inhalation fumes
3. Rhinitis medicamentosa
4. Vasomotor rhinitis

ALLERGY
1. Seasonal hayfever or pollinosis
2. Perennial allergic rhinitis

INFECTIONS
1. Common cold
2. Purulent rhinitis
3. Adenoiditis
4. Sinusitis
5. Diphtheria
6. Kartagener syndrome

ENDOCRINOLOGY
1. Hypothyroidism
2. Pregnancy
3. Menstruation

which cause his disease. Avoidance is most useful in patients with perennial allergic rhinitis in whom house dust, animal danders, molds or other household inhalants are the irritants. It is imperative to obtain a detailed environmental history. In children the area of concentration is the bedroom, because, as Deamer emphasized,[9] a child spends approximately 12 hours a day there. For a child with rhinitis secondary to house dust, we look for a feather pillow, unencased mattress, carpet, and open heating vents, all of which are sources of irritants which can be eliminated and replaced with equally functional items that will not contribute to allergic reactions. We are now training allergy paramedical persons whose work includes helping parents design hypoallergenic environments.

In considering pharmacological treatment, antihistamines are the principal agents used in the management of allergic rhinitis. They work by competing with histamine for the target cell (or, in rhinitis, the blood vessel), not by inhibiting the release from the mast cell.

Antihistamines fall into five different classes, based on their chemical structure (Table 4).[10] These are ethanolamines, ethylenediamines, alkylamines, piperazines, and phenothiazines. The side effects tend to be similar in all members of any one group. If a patient does not respond well or has side effects from brompheniramine, which is in the alkylamine class, it would be wise not to select chlorpheniramine because it is in the same class. A better choice would be an ethylenediamine such as tripelennamine. We find this chart useful because it is often difficult to remember which antihistamine is in which group.

Antihistamines are useful for rhinorrhea, nasal itch, and paroxysmal sneezing. They are not nearly as effective against nasal obstruction as a vasoconstrictor such as ephedrine, pseudoephedrine, phenylephrine or phenylpropanolamine. Frequently these sympathomimetic drugs are combined with antihistamines. Their stimulatory effect offsets the sedative effect of antihistamines. Table 5 lists some of the most frequently used combinations. We use this table as much as we do Table 4. For example, if Actifed® does not seem to be effective, we do not prescribe Dimetapp®; rather we use Rondec® which has an ethanolamine antihistamine.[10] Frequently, anticholinergic agents, either alone or combined with antihistamines and sympathomimetrics, are helpful in rhinorrhea. Examples of such preparations are Ornade® and Extendryl.®

Systemic steroids are rarely indicated in patients with allergic rhinitis. However, in a very few patients in whom the rhinitis still hampers daily activities, in spite of optimal treatment, a short course of dexamethasone sodium phosphate (Decadron®) nasal spray (marketed as Turbinaire®) often gives excellent results.[11] Turbinaire in recommended dosages has a systemic absorption equivalent to approximately 4 mg of prednisone. This can be adrenosuppressive.[12]

Immunotherapy involves giving a series of subcutaneous injections of antigen in increasing amounts with the goal of injecting the highest concentration the patient can tolerate without severe local or systemic reactions. Immunotherapy is one of the most controversial subjects in allergy. However, a double-blind study reported by Sadan, et al in 1969[13] clearly demonstrated its effectiveness in children with ragweed-induced hay fever and allergic rhinitis. This study involved 35 patients, 18 of whom were treated with immunotherapy. In Chart 1, the relative severity of symptoms is shown on the ordinate. After immunotherapy 13 of the 18 treated patients had lower scores than any of the controls.

Lichtenstein and colleagues[14] have shown that immunotherapy has three immunologic effects in allergic rhinitis. First, it causes an increase in blocking antibodies, usually gamma G and gamma

TABLE 4.—*Antihistamines*

Class	*Drug*	*Side Effect*
Ethanolamines (I)	Diphenhydramine hydrochloride (Benadryl®) Carbinoxamine maleate (Clistin®)	Pronounced sedation
Ethylenediamines (II)	Tripelennamine hydrochloride (Pyribenzamine®)	Moderate sedation, occasional nausea
Alkylamines (III)	Chlorpheniramine maleate (Chlortrimerton®) Brompheniramine (Dimetane®)	Slight sedation
Piperazines (IV)	Cyclizine hydrochloride (Tacaryl®)	Slight sedation
Phenothiazines (V)	Promethazine hydrochloride (Phenergan®)	Pronounced sedation

TABLE 5.—*Antihistamine Combinations in Common Use*

Drug	*Antihistamine*	*Nasal Decongestant*	*Other*
Actifed® Syrup	Triprolidine hydrochloride (I) 25 mg	Pseudoephedrine hydrochloride 30 mg	
Actifed® Tablet	Triprolidine hydrochloride (III) 2.5 mg	Pseudoephedrine hydrochloride 60 mg	
Dimetapp® Elixir	Brompheniramine maleate 4 mg	Phenylephrine hydrochloride 5 mg Phenylpropanolamine hydrochloride 5 mg	
Dimetapp® Extentab	Brompheniramine maleate (III) 12 mg	Phenylephrine hydrochloride 15 mg Phenylpropanolamine hydrochloride 15 mg	
Drixoral®	Dexbrompheniramine maleate (III) 6 mg	D-Isoephedrine 120 mg	
Copyrinol®	Pyrrobutamine (III) 15 mg	Thenylpyramine (II) 25 mg	Cyclopentamine 12.5 mg
Novahistine®	Chlorpheniramine maleate (III) 1.0 mg	Phenylephrine hydrochloride 5.0 mg	
Ornade®	Chlorpheniramine maleate (III) 8 mg	Phenylpropanolamine hydrochloride 50 mg	Isopropamide 2.5 mg
Triaminic®	Pyrilamine (II) 25 mg	Phenylpropanolamine hydrochloride 50 mg	
Rondec®	Carbinoxamine maleate 2.5 mg	Pseudoephedrine hydrochloride 60 mg	

M immunoglobulins (IgG and IgM) that combine with the antigen and prevent it from coming in contact with the IgE antibody.[13] Second, the IgE specific for the antigen decreases.[15] Normally in an untreated allergic person the IgE for the antigen increases during the season and somewhat decreases after the season. During the first year of treatment, IgE levels were noted to increase early in immunotherapy and then slowly to decrease. After the second year of therapy there was no rise when the pollen season started. By the end of the pollen season there may actually

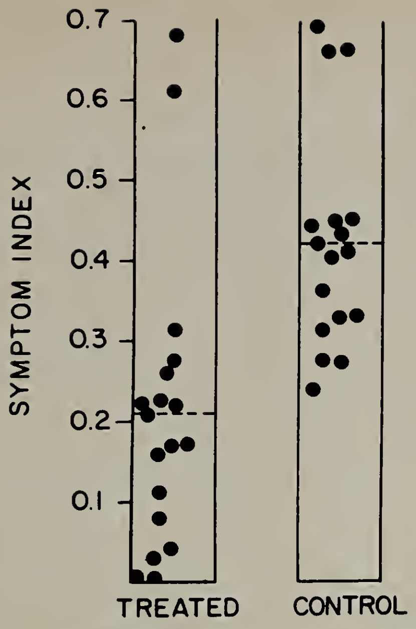

Chart 1.—Symptom indices of the 18 treated and 17 control children of Sadan's study. (Reprinted with permission from N Engl J Med (280:625, 1969).)

be a decrease in the amount of IgE in treated patients. The third effect is that after immunotherapy the ability of the cell to release histamine decreases.[13] In a manner similar to the decreased sensitivity of patients to some drugs with repeated use, immunotherapy lessens or completely stops the patient's reaction to antigen challenge.

In summary, I have reviewed with you what is known about the pathogenesis, diagnosis and treatment of allergic rhinitis, with the hope that this will aid in the treatment of this very common problem.

QUESTION FROM THE AUDIENCE: Would you comment on environmental controls. It is my impression that most of my patients whose symptoms should have improved with alteration of their environment did not seem to have been helped.

DR. MENDELSON: We find that the key is in how we instruct our patients or their parents in environmental control. Instruction sheets are seldom useful without a very specific review of the child's specific environment. In our department, Mrs. Judy Lee Bachman, who is an expert on avoidance procedures in the allergic patient's environment, makes visits to the home. Mrs. Bachman and her trainees take a detailed environmental history and, when indicated, make the home visit. On the visit, the sources of allergens in the patient's room are pointed out. Detailed advice is given on how to rid the rooms of these sources. Also the families are told where they can get any materials they need to produce hypoallergenic rooms. Each family and each referring physician is provided with a detailed report of the allergy physician's assistant's visit. We have been very impressed with the numbers of patients whose symptoms have been improved by environmental controls alone when these procedures are carefully followed.

QUESTION: Would you comment on nasal polyps and allergy?

DR. MENDELSON: Nasal polyps are very uncommon in children with allergic rhinitis. If one finds nasal polyps in a child, cystic fibrosis must be ruled out first. In an adult, one considers aspirin sensitivity. If these causes of polyps have been dismissed in a patient with allergic rhinitis, most experts feel that the polyps are secondary to a superimposed chronic infection. Unless nasal polyps are causing severe symptoms, they should not be removed because of the frequency and rapidity of recurrence.

DR. NYHAN:* In your experience, what proportion of patients do you treat with one or another of the three methods you mentioned.

DR. MENDELSON: Most of my patients are managed by avoidance therapy and pharmacological treatment. However, in a referral practice where you get only the most difficult cases, most require immunotherapy. Perhaps Dr. Hamburger would comment on this.

DR. HAMBURGER:† In a large, predominantly pediatric allergy practice where the allergists are conservative and employ allergy physician's assistants or environmentalists, I would say that approximately one-third of the patients can be managed by environmental controls. An additional third will be improved by the addition of medication. The remaining one-third will require immunotherapy as an adjunct to medications and attention to the environment. Dr. Kemp** tells me that in his experience and that of other pediatric allergists in private practice, approximately the same distribution of response to therapy is observed.

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combination of phenylephrine hydrochloride, chlorpheniramine maleate, and methscopolamine nitrate
Ornade®
combination of chlorpheniramine maleate with phenylpropanolamine hydrochloride, and isopropamide iodide
Rondec®
combination of carbinoxamine maleate and pseudoephedrine hydrochloride

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OUT, LARGE STONE!

What should be done when x-rays reveal a large solitary stone in the gallbladder?

Most surgeons agree that if it is symptomatic, a cholecystectomy should be performed. However, some believe that if the stone is asymptomatic cholecystectomy is not necessary. I believe that a large solitary stone in the gallbladder presents a real hazard. It cannot pass through the cystic duct and often if it becomes lodged in the neck of the gallbladder it produces a rapidly developing and serious group of complications. These may include acute cholecystitis, gangrene of the gallbladder, and perforation with necrosis of its wall. The stone may erode into adjacent structures, including the common bile duct, the duodenum, the stomach, the colon or the pelvis of the kidney; and it has even been reported to have eroded into ovarian cysts and through the abdominal wall.

In a series of 300 consecutive biliary tract operations I found either patent or healed spontaneous internal biliary fistules in 22 patients. This is a high incidence, higher than is usually reported, and higher than in my complete series where the incidence of spontaneous internal biliary fistulae runs approximately 3 percent. With a patent fistula and especially into the colon an ascending cholangitis can be very severe and produce marked hepatic damage. Also if a large stone passes into the small bowel it may produce small bowel obstruction. Therefore I am convinced that when a large solitary stone is found in the gallbladder, irrespective of whether it is asymptomatic or symptomatic, a cholecystectomy should be performed if the patient's condition permits.

—CHARLES B. PUESTOW, M.D., Chicago
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Refer to: Tolbutamide—Therapeutic trials and clinical practice—Medical Staff Conference, University of California, San Francisco. Calif Med 117:45-52, Dec 1972

MEDICAL STAFF CONFERENCE

Tolbutamide

Therapeutic Trials and Clinical Practice

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* All drugs are toxic; in clinical medicine we are concerned only with matters of degree. It is a basic matter of judgment in each patient whether the therapeutic advantages gained exceed the toxicity which actually occurs or the risk of the toxicity which may occur. Adverse effects of therapeutic agents may account for 10 to 15 percent of all hospital admissions. Medical Grand Rounds will be concerned today with one specific example of the difficulty in determining whether drug effectiveness outweighs possible drug toxicity as reflected in the current controversy about tolbutamide. We have asked Dr. Henry Bourne from the Division of Clinical Pharmacology to review and analyze this problem for us.

DR. BOURNE:† More than a decade ago the University Group Diabetes Program (UGDP) admitted the first diabetic patient into a massive clinical trial aimed at determining the effect of hypoglycemic agents on progression of cardiovascular disease in diabetes. In 1970, after ten years, treatment of more than 1,000 patients in 12 clinical centers throughout the United States, and expenditure of more than seven million dollars, the results became known. First in the newspapers, later in medical journals, physicians and diabetic patients read that tolbutamide and phenformin did not slow the progression of cardiovascular disease, but actually increased the rate of cardiovascular death.[1,2]

The weeping, wailing, and gnashing of teeth that ensued amounted almost to a religious war: Important gods had been defiled, including the practicing physician, the pharmaceutical industry, and the much-revered efficacy of modern drugs. More important, many diabetic patients and their physicians were anxious, confused, and frightened by the possibility that a drug they had been using for years might actually cause harm, rather than good.

Now, two years later, the smoke has begun to clear. A reasoned, critical appraisal of the UGDP study is now possible. Such an appraisal seeks answers to questions that must be asked about any clinical trial:[3,4] Are the goals of the study clearly stated? Was patient selection appropriate?

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†Henry R. Bourne, M.D., Assistant Professor of Medicine.

Were treatment regimens randomly assigned? Were end points measured by an accurate, reproducible method? Were single or double-blind procedures necessary and, if necessary, were they carried out? These questions allow us to judge the scientific validity of a clinical trial.

The practicing physician, however, puts his question more bluntly: "So what? How can I use this scientific information to treat my patients?" The "So what?" question, of course, is the real bone of contention of the UGDP study. I propose to deal with this question directly, not only because it is important for treatment of diabetes, but also because the tolbutamide controversy is the best publicized example of a common difficulty in present-day therapeutics. This difficulty is created by the ever-expanding supply of potent chemical compounds designed for treatment of an ever-lengthening list of diseases or symptoms, the etiologic and pathogenetic aspects of which are poorly understood. Essential hypertension, rheumatoid arthritis, coronary artery disease, and mental depression figure prominently on this list, along with the cardiovascular complications of diabetes mellitus. Voltaire's oft-repeated dictum takes on a disturbing ring of contemporary truth: "Doctors pour drugs, of which they know little, for diseases, of which they know less."

The modern clinical trial represents a potentially effective way of dealing with such ignorance. The clinical trial is usually superior to "clinical experience": We remember, now that we know about vitamin B_{12}, that Sir William Osler prescribed arsenic for pernicious anemia.[5] But, if a published trial is to help a physician in making clinical decisions, he must understand the trial's results and conclusions, as well as their limitations. As the tolbutamide controversy has demonstrated, the methodological subtleties and statistical sophistication of a major clinical trial can make the most abstruse molecular biology appear comparatively simple. (At least the molecular biologists appear to agree that the genetic code has been deciphered.)

Thus, the clinician's "So what?" regarding a trial of oral hypoglycemic agents may have wider implications. I hope that a careful review of the UGDP study can raise questions about the clinical usefulness of therapeutic trials in general. It may turn out, in fact, that the stimulus to asking those questions is a major, if not intended, positive result of the UGDP study.

TABLE 1.—*Criteria for Entry Into the* UGDP *Study**

1. No previous history of ketoacidosis
2. Diagnosis of diabetes no more than one year before entry into study
   (GTT or hypoglycemic therapy begun)
3. Physician's judgment of life-expectancy to be at least five years
4. Glucose tolerance test
   (Sum of four values greater than 500 mg per 100 ml)
5. Initial four weeks on diet alone:
   a. No major diabetic symptoms, including ketosis
   b. Must be able and willing to follow the study protocol

*Adapted from reference number 1.

The Study Itself

A major goal of the UGDP study was to evaluate the efficacy of hypoglycemic therapy in preventing the vascular complications of diabetes mellitus. The study's principal conclusion was that tolbutamide and phenformin actually increased the risk of cardiovascular death. Two questions are directly relevant to both goal and conclusion: 1. What disease was being treated? 2. Exactly how was it treated?

The Achilles' heel of almost any clinical study is often the selection of patients to be studied. The criteria used for acceptance of patients into the UGDP trial are summarized in Table 1. Reading them, we see that the patient population was by definition highly heterogeneous. As we shall see, this heterogeneity tends to vitiate the study's conclusions.

First, there was an attempt to obtain patients with maturity-onset diabetes (not prone to ketosis) who were newly diagnosed—that is, patients in whom a diagnostic glucose tolerance test was obtained or hypoglycemic therapy commenced not more than one year before entry into the study. Although diabetes is often a subtle, indolent disease, no attempt was made to screen out patients who already had major and widespread cardiovascular disease that might be a result of longstanding diabetes, and which was to be the major focus of attention during treatment. The proportion of such patients was, in fact, quite high (see below).

Patients judged to have life-endangering conditions which could kill them within five years were screened out since the effect of drug treatment on life-expectancy was not an initial goal of the UGDP study. This judgment proved fairly accurate since less than 10 percent of the patients were, in fact, dead after five years. But this vague criterion allowed some clinics to have a 20 percent mortality and others practically zero.

The unusual criteria applied to the glucose tolerance test also guaranteed heterogeneity. In fact, one in twenty of the patients studied did not meet even this criterion.[1,6]

The final criterion in Table 1 was meant to guarantee that the patients should not have diabetic symptoms in the absence of hypoglycemic drugs, so that a placebo group could be included in the protocol. As a result, unfortunately, potential heterogeneity was not only quite likely but guaranteed to be missed. Many of the patients had been receiving hypoglycemic therapy before entering the trial, and it is well known that the appearance of severe hyperglycemia (and symptoms) may require more than a month to reappear. In addition, this criterion meant that the principal accepted indication for any hypoglycemic treatment—the patient's symptoms—was eliminated before the study began.

Subjects who met these criteria were assigned randomly to one of five treatment groups (Table 2). All subjects were to follow a uniform diet regimen. One group received an oral lactose placebo. Three of the other four groups without regard for the individuals' blood sugar concentrations were placed on standardized doses of hypoglycemic agents: A standardized dose of insulin (based on body surface area), 1.5 grams of tolbutamide per day, or 100 mg of phenformin per day. Whatever the reasons for this experimental design, it guaranteed that 60 percent of the patients would receive treatment unlike that recommended for any diabetic patient in ordinary clinical practice. The fifth group received whatever insulin dose was required to maintain "normal" blood glucose concentration.

The effects of these five treatment regimens on the concentrations of blood glucose were completely predictable from a knowledge of diabetes and human nature. Each treatment group, including the one receiving placebo, showed an initial drop in fasting blood sugar. The placebo, tolbutamide, phenformin, and fixed-dose insulin groups showed a gradual rise in blood glucose thereafter. Fasting blood glucose remained at low concentrations only in the group for which doses of insulin were varied specifically in order to produce normoglycemia.[1,2]

TABLE 2.—*Study Treatments**

Treatment	*Dosage*
I. Lactose Placebo	Dosage schedules corresponding to those used for oral hypoglycemic agents.
II. Insulin Standard (U-80 Lente Iletin insulin)	10,12,14, or 16 units per day depending on the patient's body surface area.
III. Tolbutamide	1.5 grams per day (1 gram before breakfast and 0.5 gram before the evening meal).
IV. Phenformin	100 mg per day. 50 mg before breakfast and 50 mg before the evening meal. First week of study only 50 mg before breakfast.
V. Insulin Variable	As much insulin as is required to maintain "normal" blood glucose. The minimum dose is 5 units per day.

*Adapted from reference number 1.

The blood glucose results could hardly have come as a surprise. More surprising, in contrast, was the survival data summarized in Table 3. The proportion of patients who died, from all causes, was higher in the tolbutamide-treated group, although this difference was not statistically significant. The death rate from cardiovascular causes, however, was definitely increased—in fact, more than doubled—in the tolbutamide group. This result showed a high degree of statistical significance. The increased death rate in the tolbutamide group began to appear in the fifth year of the UGDP study.[1] A later publication showed[2] that the death rate in patients treated with phenformin was also higher than in the other groups. This result, too, was statistically significant. Hence the weeping, wailing, and gnashing of teeth.

Criticisms of UGDP Study

The many criticisms leveled at the UGDP study can be grouped under four headings:

1. *Methods and statistics.* Principal targets of many critics included the unusual glucose tolerance criteria for entry into the study; failure to obtain or adequately specify certain characteristics of the patients; analysis of mortality data on the basis of the treatment to which a patient

TABLE 3.—*Number and Percent Dead by Cause of Death in* UGDP *Study**

Treatment	Number at risk of death	Cardiovascular Cause	Other Causes	Entire Group
Placebo	205	10 (4.9%)	11	21 (10.2%)
Insulin standard	210	13 (6.2%)	7	20 (9.5%)
Tolbutamide	204	26 (12.7%)	4	30 (14.7%)
Phenformin	204	26 (12.7%)	5	31 (15.2%)
Insulin variable	204	12 (5.9%)	6	18 (8.8%)

*Data summarized from references 1 and 2. Cardiovascular causes of death included myocardial infarction, sudden death, other heart disease, and extracardiac vascular disease. For reasons noted by the UGDP investigators[2] the phenformin results are not strictly comparable to those in the other groups since this treatment was used in only 6 out of the 12 clinical study centers. Therefore, their tests of statistical significance of the increased death rate in the phenformin group were not applied to the data shown here but to results in the six clinics in which phenformin was used.

was originally assigned, despite a 12 percent dropout rate; changes in therapy in 83 of 823 patients; failure of a considerable number of patients to take drugs as prescribed; addition of the phenformin treatment group to the protocol after the first randomization had begun, leading to problems in comparing groups; the investigators' decisions to stop treatment with tolbutamide while continuing the remainder of the study; and, finally, controversial statistical methods. These issues have been discussed in detail by Feinstein.[6] The clinician may be interested in less esoteric questions.

2. *Unrealistic treatment protocols.* Three of the five treatment groups received fixed doses of tolbutamide, insulin or phenformin. These could not have been expected to produce a sustained decrease in blood sugar and, in fact, did not.

3. *Heterogeneity of the patient population.* The use of 12 widely scattered treatment centers, employing broad, vague criteria for selecting patients, led to widely differing baseline populations and death rates, the latter ranging from 19 and 26 percent in the two highest to 1 and 2 percent death rates in the lowest. As Feinstein says:[6] "Homogeneity of the population is a basic premise for the logical validity of statistical tests based on randomization; the validity of the tests cannot be assured if the population consists of a combination of markedly heterogeneous groups."

4. *Questionably random assignment of subjects to treatment groups, with possible weighting of the tolbutamide group with high-risk patients.* No critic has claimed that the actual assignment of patients into the five treatment groups was not an honestly random procedure. However, since chance alone could weight one or another group with an unusual population, it is clear that distribution of patients must actually *be* uniform as well. We know that a large number of patient characteristics can be associated with a greater likelihood of cardiovascular death. Were these characteristics significantly more common in the tolbutamide and phenformin groups? Unfortunately, the only reasonable answer to this question is, "Perhaps, but we will never know for sure."

Possible risk factors tabulated by the UGDP investigators[1] were present in a high proportion of patients admitted to the study, including: Hypertension (31 percent), lipid abnormalities (13 percent), angina pectoris (6 percent), electrocardiographic abnormalities (4 percent), history of digitalis use (6 percent), and evidence of disease of peripheral arteries (arterial calcification in 16 percent, intermittent claudication in 5 percent, and absence of one or more arterial pulses in 13 percent).

These multiple risks present numerous problems: (a) Many risks were inadequately defined or measured, including the notoriously elusive diagnosis of angina pectoris. As another example, the definition of significant electrocardiographic abnormality was changed during the study, reducing the overall percentage finally reported by a factor of three or four.[6] (b) A number of potentially important risk factors were not tabulated in the published data, although a considerable body of evidence suggests that family history, use of tobacco, or a past myocardial infarction contributes greatly to the risk of a later cardiovascular complication. (c) Those risk factors which were determined were dealt with as if they all had exactly the same significance, and as if a combination of two or more of them in one subject were not particularly important.

Feinstein undertook a painstaking investigation of the reported data, and suggested, as have other critics, that the tolbutamide group may have had a preponderance of several risk factors, especially those which were, in fact, associated with a high mortality rate. Four risk factors present in patients upon their entry into the study

TABLE 4.—*Distribution of Cardiovascular Risk Factors**

Risk Factor	*Associated Death Rate Overall (percent)*	*Prevalence of Risk Factor In Treatment Group (percent)*	
		Placebo	*Tolbutamide*
ECG Abnormal	33.3	3.0	4.0
Use of Digitalis	30.4	4.5	7.6
Arterial Calcification	22.4	14.3	19.7
Angina Pectoris	21.3	5.0	7.0

*Taken from Feinstein.[6]

(Table 4) had the highest association with the overall mortality rate, ranging from 21 to 33 percent as the study progressed. All four were present in a higher proportion of the patients in the tolbutamide group than in the placebo group (Table 4).

The UGDP investigators' answer to this criticism is a cogent one: in the tolbutamide group the increased mortality rate from cardiovascular causes remains even when all patients with any "cardiovascular risk factors" are removed from the calculations.[1] However, because so many other possible risk factors were not measured, their contention may not be valid.

Lessons of UGDP Study

The UGDP study, then, contains serious flaws, some of them irremediable. Should we, therefore, consider it a fruitless scientific debacle, best disregarded and forgotten? On the contrary, I submit that the practicing physician can learn several important lessons from the UGDP study, despite—and perhaps even because of—its obvious flaws.

Comparison of the results in the placebo with those in the variable insulin groups (Table 3) leads to an exceedingly important conclusion: Fair control of fasting blood sugar concentration achieved by flexible doses of insulin did not prevent death in a heterogenous group of patients with glucose intolerance. Therefore, the physician who uses insulin effectively to control blood sugar in an unselected group of patients with maturity-onset diabetes will not, on the average, prolong life. It is certainly possible that control of blood sugar concentration in some more homogeneous subpopulation of diabetic persons could slow the death rate, but such a subpopulation has yet to be defined. Despite all the qualifying phrases, this conclusion appears both scientifically valid and clinically relevant.

In contrast, the conclusion that oral hypoglycemic agents increase the risk of death from cardiovascular causes cannot be considered scientifically valid because of all the reasons outlined above. On the other hand, the *possibility* that oral hypoglycemic agents "cause" increased cardiovascular death is a very real one, and clinically highly relevant. It means, at the least, that future trials must test this possibility in a setting more relevant to the actual clinical use of tolbutamide and phenformin.

Here a parallel example may prove instructive. Let us assume for the moment that William Withering failed to discover the foxglove, and that ten years ago cardiac glycosides were first shown to increase myocardial contractility, although their other actions were poorly understood. Accordingly, a large multi-center trial was begun. Patients were selected on the basis of (a) no cardiovascular symptoms and (b) an unambiguous laboratory test suggesting poor myocardial contractility, such as a cardiothoracic ratio of greater than 0.5. They were randomized into two groups: One received placebo, the other 0.375 mg of digoxin per day. No provision was made for individualizing a patient's regimen, and the patients were followed until one group demonstrated a significantly greater death rate. The analogy with tolbutamide and the UGDP study is fair. The study's rationale, like that of the UGDP, would have been fairly plausible, and its methods might have proved impeccable. Nonetheless, it is a fair bet that the digoxin-treated group would die faster. In a setting where therapeutic goals are undefined and treatment is not changed to fit the individual patient, the drug's toxicity would probably outweigh its recognized beneficial effects on heart muscle.

The furor following such a digoxin trial might well cause one to lose sight of the potential clinical usefulness of digitalis. Certainly the rational clinical usefulness of tolbutamide and phenformin has received relatively short shrift in the controversy concerning these drugs and cardiovascular death. In his devastating critique of the UGDP study[6] Feinstein relegated his own opinion to a footnote. Ironically, he agreed essentially with the UGDP investigators: Oral agents should be used to treat *symptoms* from hyperglycemia; if they fail, insulin should be tried.

Who should take tolbutamide? This is really the "So what?" question leveled at the UGDP study by the clinician. I would approach this question by outlining two possible rationales for treating hyperglycemia, personified by physician A and physician B:

Physician A, concerned with preventing disease as well as treating it, seeks to prevent cardiovascular complications of diabetes by normalizing blood sugar. He will see that the UGDP study is irrelevant to his goal because the treatment protocol used for oral agents failed, predictably, to produce a sustained decrease in blood sugar concentration. He will recognize that adequate control of blood sugar concentration in a poorly selected population failed to prevent cardiovascular death (the variable insulin group), but he can claim that the results might be very different in a specific homogeneous group. Physician A will also admit that if he treats unselected patients with oral agents at a fixed dosage, without regard to their clinical response, he may run the risk of causing unnecessary cardiovascular death.

Physician B is more old-fashioned, seeking only to make his patients feel better. Unfortunately, he gets no help from the UGDP study either. The study is not relevant to his goal of ameliorating symptoms directly attributable to hyperglycemia because the patients were supposed to be free of symptoms before treatment started, blood sugar was generally not controlled with oral agents, and in the single group in which blood sugar was controlled, no assessment of symptomatic response was made (polyuria, cutaneous and other infections).

Defining Therapeutic Goals

In fact, the UGDP study presents little in the way of new clinical implications. The initial selection of patients and the unrealistic treatment regimens have made the study irrelevant to clinical practice. Still, in part because of these failings, the UGDP study may prove to have been well worth the trouble, because it should make us focus on the most crucial component of both therapeutic trials and every-day patient management: Clear definition of the goal (end-point) of treatment.

More specifically, the UGDP-tolbutamide controversy points up a fundamental difference between two kinds of therapeutic goals: Amelioration of signs and symptoms of a disease, and prophylaxis against possible future events. With oral hypoglycemics or any other drug, a physician must first decide which of these two goals he seeks, because the resulting therapeutic principles are quite different.

Before treating the signs and symptoms of any disorder, the physician first defines both his therapeutic end-point (how much better should his patient feel or function, and how fast must this be achieved?) and the upper limit of acceptable toxicity. During treatment, he can make repeated objective assessments of both efficacy and toxicity. In effect, the physician can often perform a valid therapeutic experiment, using the patient as his own control. In such circumstances, the scientific or physiologic rationale of therapy may not be clearcut, but empirical treatment can still be effective. An example might be the definite improvement in some of the symptoms of rheumatoid arthritis with salicylates although not until recently have we had any notion of how aspirin works.

Prophylactic treatment is quite different. The clinician's initial decision to institute treatment (whether tetanus toxoid to prevent tetanus or antihypertensive agents to prevent the sequelae of hypertension) must depend upon careful evaluation of evidence gathered in other patients, as well as the patient in his office. The candidate for prophylactic therapy must be representative of a homogeneous population in whom prophylaxis has proved effective. Furthermore, it will usually be impossible to prove whether prophylaxis was effective in the individual patient, unless it obviously fails. For this reason, the potential toxicity of the prophylactic regimen must be prevented if possible and detected as soon as it occurs. Even more important, in prophylactic treatment it is always useful to have an intermediate and easily measurable effect of drug treatment which can reasonably be related to the future events which the clinician aims to prevent (such as tests of blood coagulation in prevention of thromboembolism[7]).

The recently published Veterans Administration cooperative trial in treatment of hypertension[8,9] can provide an instructive contrast with the UGDP study. In the former study the level of blood pressure was used as an intermediate variable analogous to blood sugar in the UGDP study. Unlike that in the UGDP study, however, the patient population was stratified as to degree of hypertension, and randomized to treatment with effective antihypertensive drugs or placebo. Provision was made for changing the drug regimen to fit the patient. In the treated group the blood pressure did come down and stayed down. Associated with the drop in blood pressure there was a sharp decrease in cerebrovascular accidents, renal deterioration, and death.

The point of this distressing contrast between the two studies is not that one showed good results of treatment, while the other did not, but that one (the hypertension study) was designed so that the results, whatever they might be, would be clinically relevant. As we have seen, this was not true of the UGDP study.

The question, "Who should take tolbutamide?" can best be answered by considering the goals of treatment in specific subgroups of patients with diabetes. Thus, a patient prone to episodes of ketoacidosis would receive neither symptomatic nor prophylactic benefit from tolbutamide, since there is little likelihood that the drug would control his carbohydrate metabolism. Similarly, the patient whose hyperglycemia has responded to diet alone does not need oral hypoglycemic agents since he lacks a proper end-point of therapy. In all of these categories, there is little disagreement. Any toxicity from an oral agent, given in a situation where it could not be useful, is unacceptable.

In 1972 many patients whose hyperglycemia is unresponsive to diet but who are totally asymptomatic undoubtedly are taking tolbutamide. Since no physician would justify such treatment in order to rectify laboratory values alone, hypoglycemic therapy in these patients must be (in theory, at least) prophylactic—that is, aimed at preventing future events. The voluminous and controversial literature[10] relating pharmacological control of blood sugar concentration to the prevention of cardiovascular complications of diabetes is far from convincing, especially if subjected to the kinds of criticism leveled at the UGDP study. I personally would withhold drug therapy in this group of patients while fully recognizing that eventually a subgroup of diabetic patients may be shown to have fewer myocardial infarctions and peripheral vascular occlusions, or less progressive retinopathy if given prophylactic hypoglycemic treatment.

For patients whose hyperglycemia *is* at present *symptomatic*, such as with increased infections, polyuria, polydipsia, or transient visual disturbances, an oral hypoglycemic agent (or insulin) is probably indicated. It should, of course, only be continued as long as both symptoms and blood sugar remain improved. In addition, it may be useful to stop the treatment periodically (every six to nine months) to determine whether it was really needed. Finally, it must be recognized that "secondary failure," or recurrence of hyperglycemia after initial improvement on drug treatment, will occur at various times in a high proportion of patients.[11] If this does occur, and if the patient truly needs normal blood sugar to prevent symptoms, he should then receive insulin.

The True Value of the UGDP Study

Despite all the criticism stimulated by the UGDP study, its real achievements should be measured in comparison with the explicitly stated goals of the UGDP investigators: 1. To evaluate efficacy of hypoglycemic treatments in prevention of vascular complications of diabetes; 2. To study the natural history of vascular disease in patients with maturity-onset diabetes not dependent on insulin; 3. To develop methods applicable to cooperative clinical trials.[1] As we have seen, the first two goals were compromised by heterogeneity of the patient population, possible nonuniform distribution of cardiovascular risk factors, and inappropriate treatment protocols. Nonetheless, the demonstration that control of blood sugar with insulin did not prevent cardiovascular death represents a real contribution to medical knowledge.

The contention that oral hypoglycemic treatment confers an increased risk of cardiovascular death cannot be considered proved by the evidence presented, primarily because we will never know whether cardiovascular risk factors were uniformly distributed among treatment groups. In retrospect, this problem could have been avoided by more careful definition and assessment of risk factors upon entry of patients into the study, perhaps combined with some stratification procedure (analogous to that employed by the Veterans Administration study of antihypertensive treatment). This then might have allowed comparison of results of treatments in comparable patient populations. Even here, however, the UGDP study has made a potential contribution to modern therapeutics by highlighting an often neglected principle: Any potent drug administered in a rigid fashion, without regard to the patient's response, carries with it the possibility of serious toxicity but little possibility of benefit to the patient.

Finally, both in spite of and because of its faults, the UGDP study has indeed contributed to the future development of methods applicable to large cooperative clinical trials. We have learned the importance of relative homogeneity of patient populations, uniform and random distribution of specific patient variables among treatment groups, realistic treatment protocols applicable to medical practice, and the need for designing a clinical trial so that the practicing physician's "So what?" can be met with a straightforward answer. If we can use these lessons effectively in the future, the effort and expense of the UGDP study will not have been wasted.

TRADE AND GENERIC NAMES OF DRUGS

DBI-TD®	phenformin
Orinase®	tolbutamide

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—JOHN C. CARDONA, M.D., New York City
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Important Advances in Clinical Medicine

Epitomes of Progress -- Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Radiology. Each item in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Radiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panels to the Section on Radiology of the California Medical Association and the summaries were prepared under their direction.

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Indications and Value of Coronary Arteriography

As CORONARY ARTERIOGRAPHY becomes more universally available, indications for this potentially morbid procedure must be considered critically. The indications may be divided into three groups:

1. *Heart Disease of Unknown Cause*—This includes congestive heart failure or cardiomyopathies of undetermined cause and recurrent ventricular arrythmias. This group with potential end-stage disease may be improved if an applicable lesion is found.

2. *Diagnostic Problems*—This includes chest pain not defined by routine studies such as treadmill EKG, upper intestinal and gallbladder studies, and obvious pulmonary parenchymal or chest wall disease. There must be sufficient need to rule out coronary artery disease to undergo the risk of the procedure in these patients. Reports have shown up to 5 percent of patients with atypical pain have significant coronary artery disease.

3. *Presurgical Group*—Patients with a history of myocardial infarction, positive treadmill tests, or abnormal EKG, who also have disabling angina or angina of increasing severity (pre-infarction angina). Patients with non-disabling angina, asymptomatic ischemic changes on EKG or treadmill tests, or patients adequately managed by drug therapy are not studied, as the protective aspects of aorto-coronary bypass have not been proved.

Complications of the procedure will vary in different series. At Stanford University Hospital, overall mortality for approximately a thousand cases is .8 percent. Major complications considered included myocardial infarction 1 to 1.5 percent, femoral thromboses 3 percent, cerebral vascular accidents .8 percent.

The final consideration before proceeding with coronary arteriography should be the potential benefit to the patient. These may be improved medical management whether medicinal, dietary, or perhaps change in overall life style. The other benefits include immediate surgical improvement of disabling and potentially mortal disease. Several present-day surgical series suggest profound improvement in symptoms and return to normal activity. It remains to be seen how long the improvement lasts in the large number of patients operated upon.

One must, therefore, critically assess the indications, risks, and potential benefits to each patient individually before submitting him to coronary arteriography.

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Efficacy Studies:
Skull Radiography in Head Trauma

The role of skull roentgenograms in management of head trauma has been critically reviewed. Fractures are demonstrated in a small percentage and only rarely does the presence of fracture, by itself, modify treatment.

Fractures were demonstrated in 6.2 percent of 1500 patients of all ages (Seattle, 1969-70) and were pertinent to treatment (antibiotics for basal fracture, elevation or removal of depressed fragments) in 28 of the 93 patients.

Fractures were demonstrated in 8.6 percent of 570 children (Kansas City, 1969). The type and location of fracture had no important bearing on symptoms, physical findings, treatment or the need for hospitalization. Involvement of the middle meningeal groove or sagittal sinus was not significantly related to concussion, severe symptoms or subdural hematoma. The mere presence of fracture affected treatment in two of forty-nine patients.

The cranial contents may sustain severe injury within an intact skull, and bone injury seldom affects treatment. Skull radiography is requested more out of habit and concern over possible medico-legal implications than as a specific guide to treatment. More critical appraisal could result in substantial savings of time, money and radiation exposure without jeopardizing patient care.

Vernon R. Gee, m.d.

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Coronary Arteriography in Acute Myocardial Infarction

Previously it has been recommended that left heart catheterization and coronary arteriography not be performed less than three to four months after acute myocardial infarction. However, recently several institutions have successfully undertaken coronary arteriography in critically ill patients with acute myocardial infarction. It is now realized that recent myocardial infarction is only a relative contraindication to coronary arteriography and that if a patient's condition is critical enough to warrant surgical intervention, coronary arteriography may be relatively safely undertaken.

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Asbestosis—Diaphragmatic Pleural Calcification

Isolated calcifications limited to the diaphragmatic pleural surface can occur after a latent period of approximately 20 years, following only a brief period of occupational exposure to asbestos. Asbestos is used commercially in approximately three thousand items and the general contamination of the urban atmosphere by asbestos is now a matter of public concern. Furthermore there is also an increased incidence of pleural and peritoneal mesotheliomas, bronchogenic carcinomas, and gastrointestinal neoplasms occurring from 24 to 53 years after the initial exposure to asbestos dusts.

When diaphragmatic pleural calcifications are found, particularly bilaterally, with no other evidence of pleural thickening or interstitial disease, and no evidence or history of trauma or infection, exposure to asbestos dust should be considered the etiologic factor. It is incumbent upon the radiologist to suggest the diagnosis of pulmonary asbestosis and to press for a detailed occupational history.

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Hodgkin's Lymphomas Revisited

Gilbert, and later Peters, realized the advantage of radiating contiguous, clinically uninvolved lymph nodes as prophylactic therapy in Hodgkin's disease management. Recently, "contiguity" has been extended to include spread via the thoracic duct in either direction. Megavoltage radiation therapy units paved the way for use of large radiation fields because these units could deliver a uniform flat field of radiation exposure with precise cutoff at the margins and with minimal skin and systemic reactions. A total-nodal approach to radiation therapy of Hodgkin's disease paralleled the development of megavoltage equipment. In this technique, all major lymphoid pathways of dissemination are prophylactically treated. Treatment fields are carefully shaped to include all primary node systems, while excluding normal uninvolved tissue. Bone marrow in the axial skeleton is shielded whenever possible to preserve production of blood-forming elements. Preservation of a small percent of bone marrow reserve may become crucial if the patient must receive subsequent chemotherapy. Randomized clinical trials at Stanford, under Dr. Henry Kaplan, have demonstrated increased survivals for each stage of disease following total-nodal radiation therapy. The overall five-year survival for all stages of disease as of October 1971, was 78 percent. The five-year relapse-free survival rate for Stage I and IIA was 90 percent.

Abdominal exploration with splenectomy and biopsy of liver and para-aortic nodes gives accurate staging as well as valuable prognosis. Evidently lack of splenic involvement means lack of liver involvement. Splenectomy plus multiple liver and node biopsy helps the radiotherapist to establish radiation ports and assists the hematologist in determining the advisability of chemotherapy. Splenectomy also helps the radiotherapist avoid complicating radiation nephritis in the left kidney.

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Physiology and Significance of the Prolonged Nephrogram

The nephrogram phase during intravenous urography refers to the radioopacity of the renal tissue exclusive of the calyces and renal pelvis. The nephrogram is usually most intense during the first five minutes following injection of the contrast material, with subsequent progressive decrease in intensity over the next several hours.

An abnormally prolonged intense nephrogram is frequently observed in patients with obstructive uropathy. Recent experimental evidence suggests that glomerular filtration continues at a reduced rate, even in the presence of complete obstruction. Continued filtration of contrast material in the face of tubular resorption of salt and water probably accounts for the prolonged intensified nephrogram that is observed.

A prolonged nephrogram is also obtained when intravenous urography is performed in a patient with systemic hypotension. The mechanisms involved may be similar to those postulated for the obstructive nephrogram; a decidedly reduced glomerular filtration combined with excessive salt and water resorption leads to a progressive accumulation of contrast material within the tubules.

Melvyn Korobkin, M.D.

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Hypertension Caused by Constricting Renal Lesions ("Page Kidney")

Hypertension can be produced by lesions which externally compress the kidney (Page kidney) without associated major renal artery narrowing (Goldblatt kidney). The mechanism for producing the hypertension is probably renal ischemia since abnormal split function studies, radionuclide renograms, and renal vein renin ratios have been found.

Sub-capsular and peri-renal hematomas, or scars, presumed due to previous trauma, are the most frequent cause of this entity. Excretory urography and renal arteriography can demonstrate compression of the collecting system and intrarenal arteries by an avascular intrarenal mass, without renal arterial narrowing. Diagnosis is suspected by an appropriate history of trauma (in some, but not all, cases) and abnormal radiographic findings; and substantiated by appropriate function studies. Surgical intervention (nephrectomy, hematoma evacuation) provides opportunity for cure of the hypertension in some patients.

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Vascular Changes Associated With Drug Abuse

Arteriographically demonstrable changes in the arteries supplying several organs have been described as a more than casual accompaniment of drug abuse. These arteriographic changes consist of microaneurysms, indistinctness of vessel outlines, irregular segmental narrowing, and partial or complete occlusion. The kidneys and abdominal viscera have demonstrated these changes, at times in patients without symptoms referable to these organ systems; and similar changes in the brain have been noted in patients with neurological abnormalities. Histologic material in some cases has shown a necrotizing angiitis such as is found in polyarteritis nodosa. It is theorized that drug abuse causes a necrotizing angiitis although the specific causative drug(s) is not definitely known.

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Diagnostic Ultrasound in the Diagnosis of Renal Masses

Ultrasonic B-scanning, which produces a two-dimensional tomographic display of the internal body structures, is capable of radically altering the conventional approach to renal mass lesions. If the excretory urogram indicates a mass, utilizing this method will show the size, position, and consistency of the lesion with 95 percent accuracy. Cysts as small as 2 cm in diameter are readily recognizable. If a typical cyst pattern is observed, direct puncture is employed, using the skin coordinate obtained from the ultrasonic scan. Transducers with central holes for needle insertion are now available to further insure accurate insertion. The cyst fluid may then be analyzed for malignant cells and fat content, and at the same time contrast is injected into the cyst to demonstrate its smooth inner lining. Cyst puncture may be performed as an outpatient procedure.

If the ultrasonic pattern is that of a solid or is indeterminate, selective renal angiography is performed to define the lesion, its arterial supply, and venous drainage.

By employing the ultrasonic scan, a large number of renal arteriograms can thus be avoided with no loss in diagnostic accuracy.

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The Role of Lymphangiography in Ovarian, Cervical, Endometrial and Prostatic Cancer

Terry et al, have pointed out the value of lymphangiography in the initial staging of patients with carcinoma of the uterine cervix. The lymphangiograms were positive in 25 percent of Stage II-B, in 48 percent of Stage III-A, and in 75 percent of Stage III-B. In Stage III cervical disease, the para-aortic lymph nodes were positive in 17 percent of cases. The study is very valuable in determining how extensive the radiation therapy should be and also helpful in discovering recurrent disease.

Hendricksen, Beck, and Latour have made studies of patients who have died from endometrial carcinoma. They found a high percentage of metastases to the para-aortic lymph nodes at autopsy and that a significant number of patients had para-aortic lymph node involvement with negative pelvic lymph nodes.

In a series, studied by Hanks and Bagshaw, of patients with ovarian carcinoma who had lymphangiography, the staging and the treatment planning was changed on the basis of the results from this examination. In seven of twenty-two selected patients, the para-aortic lymph nodes were involved.

Very little emphasis has been placed on the involvement of the lymph nodes from prostatic carcinoma. Since many patients with locally advanced prostatic carcinoma are now being irradiated with "curative" tumor doses, it is important to know the extent of the disease in order to adequately plan the treatment portals.

If the extent of the disease is not known, then it cannot be adequately treated. Too often patients have been subjected to extensive surgical or radiation therapy, or both, without the true extent of the disease being known. If the para-aortic lymph nodes are involved, then the usual plan for radiation therapy will have to be modified and also extensive radical operation for recurrent or persistent disease may not be feasible.

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Non-Operative Retained Biliary Tract Stone Extraction

Retained, overlooked, or forgotten stones present a common problem in operations on the biliary tract. If duct stones are discovered on post-operative T-tube cholangiography, a second surgical procedure is usually required. This reintervention, with its higher morbidity and mortality than the original surgical procedure, can be avoided by the use of a new roentgenologic technique—non-operative retained biliary tract stone extraction through T-tube tract.

The T-tube is left in place for about five weeks after operation in order to form a fibrous tract. After its removal, a flexible catheter is then introduced into the duct system through the T-tube tract. Ureteral stone baskets, wire slings, or extraction forceps manipulated through the catheter are utilized for stone extraction.

During the past year we applied this ambulatory procedure in 16 patients with retained biliary tract stones. The procedure was unsuccessful in one case. Stones were extracted in the others, and all 15 patients were asymptomatic after stone removal in three to nine months of follow-up.

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Mazzariello R: Removal of residual biliary tract calculi without reoperation. Surgery 67:566-573, Apr 1970

The Angiographic Diagnosis of Gastrointestinal Bleeding

Diagnosis of the site of gastrointestinal hemorrhage is often difficult. The usefulness of selective arteriography in locating the source of gastrointestinal bleeding has been demonstrated. Bleeding as slow as 0.5 ml per minute has been localized in experimental animals. Selective angiography is particularly useful in determining bleeding sites in sections of the gastrointestinal tract which are difficult to endoscope—the small intestines and colon. In 27 patients with acute rectal hemorrhage and noncontributory sigmoidoscopy, selective angiography demonstrated a bleeding point in 18. In 13 patients, the hemorrhage was secondary to diverticulosis and in 12 of the 13 the bleeding was located to the right of the splenic flexure. Precise localization of the offending diverticulum allowed the surgeon to perform segmental colon resection. Selective arteriography is often the only effective way of diagnosing the source of chronic colonic and small intestinal bleeding caused by arterial-venous malformations. In one study three-quarters of the patients had a laparotomy which failed to reveal A-V malformations that were subsequently viewed when selective angiography was used. Bleeding from the second and third parts of the duodenum is difficult to localize by endoscopy and barium roentgenography, but bleeding stress ulcers in the mid-distal duodenum may be readily localized angiographically.

The value of selective catheterization in the bleeding patient with varices is two-fold. Angiography may demonstrate a nonvaricocele source of hemorrhage, such as an ulcer. If no source of arterial hemorrhage is found, and portal hypertension with collateral varicocele channels is demonstrated, selective vasopressin infusion through the arterial catheter will often control the active varicocele hemorrhage.

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Physician Power

There can be no doubt that a growing number of practicing physicians are beginning to feel uneasy, insecure, frustrated, and sometimes even resentful, as they try to render what they believe to be good professional care in a practice environment which to them appears to be increasingly hostile. There is obvious dissatisfaction with the amount of influence the profession has so far been able to bring to bear in this rapidly changing and often quite threatening situation. There is a growing belief that some sort of confrontation between the medical profession and the practice environment (which includes both the public and private sectors) has become inevitable, and that the power position of physicians is at present inadequate to influence the course of events sufficiently so that the essentials of good patient care can be preserved and enhanced. All of this has progressed to the point where some physicians who have fought hardest to uphold the principles of freedom and self-determination in patient care are now willing to forego these principles and to don the yoke of unionism in the hope of being able to present a united and strong front when the tests of strength, which they believe are now inevitable, finally arrive. All of this is very disturbing and it is certainly not a good thing for medicine or for health care in this nation. Uneasy, insecure, frustrated and resentful persons do not generally perform at their best, and inevitably they look around for some sort of power or other means to improve their situation.

The reasons for this uneasiness and dissatisfaction are well known to practicing physicians but may not be so to many outside the profession. Few besides physicians read these columns, but some do, and for them a few of the more important causes are mentioned herewith. A profession which has developed the best trained physicians in the world, which offers the most advanced medical care and whose educational institutions are a mecca for foreign scholars is finding itself berated almost daily because all the people do not receive all its services. More, the profession is illogically held responsible for staggering and still rising costs over which it has no real control, unless physicians were simply to deny their patients needed services. It is castigated for not preventing health care problems that are social rather than medical in origin. Federal and third party money has destroyed the privacy of the relationship between a physician and most of his patients and with it much of the satisfaction that both formerly derived from this relationship. Court decisions and court awards in matters of professional liability are increasingly based on a simplistic legal doctrine called *res ipsa loquitur* which physicians know is by no means always valid in the real world of medical practice and human biology. Physicians feel that many of these court decisions are unjust, not only to physicians but to society as a whole, and there is no doubt that they often add significantly and unnecessarily to the cost of medical care for which physicians are then blamed. One can go on. Practicing physicians are now held by government fiat to 2.5 percent fee increases while everyone else, including their employees and landlords, is allowed 5.5 percent. And there is no evidence of any sort of ceiling on the price a physician must pay for professional liability insurance in the face of unpredictable court decisions. Not only is this economic bind unjust, it has begun to be crippling for most practicing physicians. There is a belief held by government and others that physicians make too much money, but physicians know that if a plumber worked the same number of hours and the same kinds of days most physicians do, he would earn as much in a year as does the average physician. So all together, it is little wonder that physicians are beginning to feel put upon, disgruntled and insecure, and even somewhat resentful toward the environment in which they must practice.

What is to be done about all this? How should the medical profession respond? What sort of countermeasures will be effective in this kind of practice environment and at the same time strengthen good medical practice and good patient care? Physicians have one enormous strength. They still stand high in the public esteem, and as much or more than any other group they enjoy the trust of the public. If the public does not lose its esteem for physicians and if the trust is not violated, this is the true source of physician power to influence the practice environment which can be brought to bear. It is waiting to be tapped. The situation in which physicians find themselves clearly calls for countermeasures but if these are to be successful they must derive their strength from the esteem and trust which the public has for its physicians. In general the countermeasures which have so far been proposed or undertaken by the medical profession have fallen short of really bringing physician power to bear. In California, however, some of them have begun to be productive. The direct involvement and participation of the California Medical Association in many public and voluntary health care enterprises, and in informing the public, has begun to develop some real public understanding and support for the CMA and its programs. Some measurable public support has begun to develop for CMA's pioneering peer review and continuing education programs. Its legislative program has achieved considerable success and has come to be both appreciated and respected by state and national legislators. But, successful as all this has been, it has not yet been enough to bring physician power to bear to the extent necessary to effectively counteract prevailing trends in the present day practice environment with all that they imply for increasing difficulties for physicians in providing good patient care.

In the March issue "A Power Base for Medicine" was discussed in these columns. The medical profession was identified as the life force in medical and health care, and public opinion as the tap root of physician power, whether one is speaking of influence or of various kinds of pressure, or of the scientific, social, economic or political arenas of medical and health care. Some methods by which the medical profession can develop public opinion as the tap root of physician power and exercise various pressures were discussed. More recently, at the Component Society Officers Conference the president of the California Medical Association addressed himself ably to this subject and identified practical ways physicians and the medical profession may exercise their influence. But essential as all this is for physician power, it seems clear that something more is now needed. The following is suggested:

First, a common purpose must be identified which will both unite the profession and gain the support of public opinion. This must be something which will unite all physicians regardless of age or political philosophy and gain their wholehearted support. "Private practice," which has been the traditional rallying cry of organized medicine, is no longer sufficiently all-embracing. It now means quite different things to different people and in fact is only one of a number of accepted methods of rendering patient care. Nor does unionization of the profession seem likely, so far, to meet this need. Where, then, can one find a true common purpose to which all physicians can repair? It would seem that it should somehow be rooted in the particular knowledge and expertise of physicians as these can be applied to patients and to society as a whole. Physicians are society's specially trained experts on human health and its disorders, and their professional life work is to improve health and treat its disorders. In connection with their training and practice all physicians are particularly aware of the biological and social uniqueness of every individual and the relationships of this uniqueness to the individual's health and its disorders. It is suggested that in this may lie a true common purpose for all physicians: to focus upon the biologic and social uniqueness of every patient and every person and to bring their special knowledge and special expertise in the ramifications of this uniqueness to bear not only to improve the health of those who come under their care but to promote solid scientific and social progress for the betterment of human health. A common purpose such as this would seem entirely compatible with the science and practice of medicine as we know it, and worthy of the wholehearted dedication of a great profession united to serve its patients and society as a whole.

Second, if such a common purpose can be found with which all physicians could identify, whether in practice, training, teaching, government or wherever, and if it can gain public support as well, there will then have been created a solid base upon which to build a technology of physician power. There is considerable evidence that knowledge is power, involvement is power, money is power (and, by the way, it is possible to use other people's money to exercise power) and public support is power. Given a common purpose, the technology for use of these forms of power readily can be developed and applied in the scientific, social, economic and political arenas of health care.

Third, it is quite apparent that physician power can be exercised most effectively through teamwork. While physicians may be the leading professionals when it comes to knowledge of health and its disorders, they share with others their recognition of individuality in human nature, and share with many others their commitment to the betterment of human health and well-being. Teamwork is certainly essential for the efficient and effective exercise of physician knowledge and physician power. There is and must be teamwork in patient care, teamwork in health care, teamwork in public education, teamwork in achieving high quality care and cost benefits for physicians and patients alike, and teamwork in achieving political and legislative goals. There must be teamwork within the profession and with others, including government, if physician power is to find full expression.

Physician power of this kind can become a potent force for the betterment of health care in this nation and, if properly developed and exercised, it can achieve results which will go far to reduce insecurity, frustration and resentment among practicing physicians in the care of their patients. But there must be an identifiable purpose that is acceptable not only to the vast majority of physicians but to the public, there must be better development of a more sophisticated technology for the use of physician power, and there must be an even greater recognition of the importance and implications of teamwork in support of the common purpose.

—MSMW

Allergic Rhinitis

ALLERGIC RHINITIS AFFECTS one and one-half million Californians and over 13.5 million Americans.[1] Further, there is a similar number of persons receiving anti-histaminic drugs for mild but annoying nasal symptoms, many of which are related to allergic sensitivity. Such people are not working at their peak efficiency due to impaired sleep and drug side effects. A complication of allergic rhinitis is serous otitis which affects two and a half million American children and causes partial deafness and difficulty in learning.[2] Allergic rhinitis, then, is a leading health problem in numbers of Americans affected, and the costs in outlays for drugs, in reduced working efficiency and in personal comfort are huge.

In the conference reported elsewhere in this issue by Mendelson et al, the mechanism of immunoglobulin E-mediated allergic reactions is reviewed, especially with regard to classical allergens such as pollen, house dust and animal danders. Further, they point out the "priming effect" of a heavy exposure to ragweed pollen antigen which causes fragmentation of the nasal basement membrane which makes the nose vulnerable to much smaller exposures of pollen and other allergens.[3] This may occur with other allergens also and may account for the common cyclic occurrence of allergic symptoms, especially in California, where seasonal swings in pollen counts are less pronounced but pollens occur the year around. The authors also refer to milk and other foods which may cause allergic respiratory symptoms, often also on a cyclic basis. Further, they mention elevated serum IGE in a patient with hayfever. Several methods utilizing radiolabeled antigens or anti-IGE sera are proving useful in quantitating specific IGE antibodies in allergic patients.[4,5] These are useful in following a patient's course during treatment.

It must be emphasized, however, that not all rhinitis is allergic, as is illustrated by vasomotor rhinitis, for which the precise pathogenic mechanism is unknown. Often such cases are labeled "allergic" for want of a diagnosis, and temporizing anti-allergic therapy is given with negative results. This calls into question all such therapy in general. Connell[6] described "nasal mastocytosis" in non-allergic patients who had abundant histamine release and rhinitis. Other investigators[7] are describing specific nasal pathophysiology which removes other cases from the diagnostic discard bag of vasomotor rhinitis.

Under specific therapy for allergic diseases, avoidance of the antigen, where possible, is still the cardinal principle. The UC, San Diego, group have begun a unique and important program of training paramedical specialists in environmental control; such persons can point out to the patient in his own home specific sources of possible allergens and how to avoid them. Such environmental technologists should be a great asset to allergists and other physicians in private or clinic practices.

Immunotherapy for allergic diseases remains under attack for efficacy despite its 60-year history.[8] However, in ragweed hayfever, "the purest form of allergy," a number of double-blind studies have shown unequivocal improvement at statistically significant levels[9,10] in treated patients compared with placebo-treated controls.

Non-specific therapy includes classical use of nasal decongestants and anti-histaminic drugs which compete with histamine for receptors in nasal vessels. With the demonstration that β-adrenergic agonists raise cellular levels of cyclic 3′5′ adenosine mono-phosphate (AMP) which inhibits histamine release from sensitized human leukocytes, there is renewed interest in these agents in all allergic diseases, including allergic rhinitis.[11] Disodium cromoglycate inhibits histamine and SRS-A release from human lung mast cells in asthma and appears to be useful therapeutically.[12] Therefore, its use in allergic rhinitis is also being explored, so far with variable but some promising results.[13,14]

Over the past decade, great strides have been made in defining the immunologic and pharmacologic mechanisms of allergic reactions which are being now translated into new and effective treatments.

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The Treatment of Acute Myelocytic Leukemia

IN 1961 COMPLETE remission (CR) was achieved in only 5 percent of patients treated for acute myelocytic leukemia (AML).[1] Since the development and use of cytosine arabinoside and daunomycin, increasing remission rates have been reported.[2,3] The paper of Poth et al in this issue of California Medicine also reports higher remission rates but stimulates many questions concerning the treatment of AML. While the authors address themselves to the achievement of remission, the reader should bear in mind that the ultimate goal of treatment is not only remission but survival of good quality.

In 1966, Dameshek et al[4] reported that patients with "smoldering" acute leukemia lived longer than those who achieved complete remission, and concluded that there was no constant relation between achievement of remission and length of survival. With newer treatment programs, Dameshek's conclusions of six years ago may be invalid today, but it is still necessary to evaluate the quality and length of survival beyond the achievement of remission before the effectiveness of therapy can be judged. A program in which all patients achieve remission but die the next day is obviously inferior to one in which 50 percent of patients who achieve remission go on to a prolonged survival. One can also ask how well the remission-inducing regimen prepares a patient for maintenance therapy and survival.

With this in mind, and with some mathematical machinations, we can examine the significance of the 17 percent CR rate of daunomycin with the apparently superior 44 percent CR rate of the combination of cytosine and thioguanine reported by the Stanford group. Among those who responded, the mean duration of CR after daunomycin treatment was 10.6 months (median 10.2), while the mean duration of CR for the cytosine-thioguanine group was 5.8 months (median 3). For all who were treated with daunomycin, the mean duration of CR was 1.8 months (median 1.7) and among all patients treated with cytosine-thioguanine, the mean duration of CR was 2.6 months (median 1.3). The importance of a seemingly great increase in effectiveness of the combination of cytosine and thioguanine over daunomycin alone in inducing remissions shrinks when we realize that the increase in mean duration of remission for all patients treated was only 0.8 months. This pales to a *decrease* in the median duration of remission for all patients when the cytosine-thioguanine group is compared with the purportedly inferior daunomycin group.

This may be playing with numbers, but it does point up the fact that, especially in AML, before we can make a significant contribution to survival we have to develop maintenance regimens which will hold patients in effective remission. Induction of remission is a necessary prerequisite to prolonged survival, but it is only a first step, no more. The greater problem is placed at the doorstep of the chemotherapist—to devise effective cyto-reduction programs with improved maintenance, in order to achieve the goal of prolonged survival.

Another sobering numbers game is suggested by examination of the mortality data in the paper of Poth's group. In order to achieve CR with daunomycin in four patients out of 23, the authors conclude that 12 others died as a result of the treatment. In the superior Ara-C-thioguanine group, six drug-related deaths occurred to achieve CR in eight patients. This is a drug-induced mortality of 52 percent and 33 percent, respectively. Overwhelming treatment-caused mortality is the basis of some argument against therapeutic intervention in selected patients with AML. This kind of medical brinksmanship can be defended only because of the certain mortality for all patients with this disease and the possibility that in some the disease may be palliated for "significant" periods of time. Further, if we are ever to find a means of control or cure, we are obligated to try reasonable and scientifically conceived therapeutic programs.

On this basis, some observers would also challenge the authors' statement that patients with AML should be treated on general medical services. An alternative would be initial immediate referral to special leukemia study centers, where patients can be allocated to carefully randomized therapeutic protocols and started on therapy, after which patients can be cared for in their own locale for at least part of their illness.

The treatment of AML has now reached the stage at which acute lymphoblastic leukemia was in the early 1960s. The disease process can be altered. We must now proceed with the task of prolonging remission and, with it, survival. Perhaps acute lymphoblastic leukemia can also serve as the model to treat AML—that is, with the intent to cure.

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A Refreshing Approach

Elsewhere in this issue is an account of how a diverse multi-ethnic community succeeded in establishing a health center to meet its needs. The approach was quite different from that now generally being used to establish a neighborhood or community health center, and it is worth noting that so far at least it appears to have been more successful than many.

The key to this success seems to lie in the source of the energy behind the effort. This clearly came from within the diverse multi-ethnic community itself which wanted to do something, and not from the government or the "establishment" or anyone else who wanted to plan whatever it was they thought best for that particular community. The energy came from a recognition of a need where the need was, and from a determination to fill that need somehow.

Also essential to success was the manner in which this "grass roots" energy was applied. This diverse community wisely said, "How will you help us?" rather than "Why haven't you helped us?" The result was a warm and effective response from those who could help. Physicians, other providers and a variety of agencies and organizations both public and private joined together with this diverse multi-ethnic community, and Our Lady of Guadalupe Health Center became a going thing.

One is tempted to identify this approach as the American way of solving community problems. Indeed it is the traditional American approach and it is refreshing to know that it still works. But there is much to suggest that the traditional American way has been changing. In recent years there has been enormous public support of efforts to plan and solve a variety of community problems for its citizens, and enormous amounts of money are being spent to try to make the approved solutions work. Many Americans endorse this approach and some may even be convinced that this has become "The American Way." But so far planning for communities by outsiders has not worked very well. Perhaps this is because the source of energy is from without instead of from within. In any case the value received for dollars spent has been disappointing. There may be a lesson for us all in the refreshing approach of Our Lady of Guadalupe Health Center.

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CASE REPORTS

Refer to: Rom WN, Benner EJ: Toxicity by interaction of tricyclic antidepressant and monoamine oxidase inhibitor. Calif Med 117:65-66, Dec 1972

Toxicity by Interaction of Tricyclic Antidepressant and Monoamine Oxidase Inhibitor

WILLIAM N. ROM, M.D., AND
E. JACK BENNER, M.D., *Davis*

A PATIENT RECENTLY SEEN at the Sacramento Medical Center had a hyperpyretic crisis and then shock caused by the incompatible interaction of tranylcypromine (Parnate®) and desipramine (Norpramin®). Monoamine oxidase inhibitors are known to interact with sympathomimetic amines to produce hypertensive crises, to potentiate the effects of various central nervous system depressants (for example, narcotics, alcohol, barbiturates) and to produce various acute crises when given with central nervous system stimulants.[1,2,3] The problem of avoiding these deleterious drug interactions is magnified when patients do not remember what medications they are taking, nor for how long they have taken them, as in the following case.

Report of a Case

A 60-year-old white woman was admitted to the psychiatric ward of the Sacramento Medical Center (SMC) in August, 1970, for evaluation of involutional depression. She was given amitriptyline (Elavil®) and discharged to the care of her private physician. Subsequent medications included thyroid extract, 1 grain daily, hydrochlorothiazide, 50 mg daily, ethachlorvynol (Placidyl®) 750 mg for sleep, and tranylycypromine (Parnate) 10 mg twice daily, starting in early November, 1971. On November 19, 1971, she came to SMC complaining of weakness and fatigue. She was thought to have a depressive neurosis since she was acutely upset and unable to remember her medications. She was given desipramine (Norpramin) 50 mg tablets to be taken thrice daily.

On November 26, 1971, her son brought her to SMC because of fever. She was agitated and her behavior bizarre but on examination no other abnormality was noted. The white blood cell count was 7,900 per cu mm with 68 percent neutrophils; the hemoglobin, hematocrit, blood glucose, blood urea nitrogen, serum sodium, potassium, chloride, and bicarbonate values were all within normal limits. Since none of the previous history of illnesses or medications was known, the cause of the fever was not clear. Therefore, the patient was placed in the observation unit for the night. At 4 a.m. her rectal temperature was 104° F, she had pronounced hyperreflexia and flexor plantar reflexes, and she was disoriented as to time, person, and place, with increasing confusion and agitation. She was transferred to an in-patient ward. The rectal temperature rose to 107.6° F, and cooling was instituted immediately. Further examination demonstrated pronounced bilateral nystagmus, mydriasis, opisthotonus, bilateral Babinski signs, a gross tremor with muscle twitching, and obtundation. The cerebral spinal fluid was clear and the chemical values within normal limits. An electrocardiogram showed no abnormality but sinus tachycardia. Nasogastric tube aspirate was initially hematest-positive but cleared, and no capsules were returned. Arterial blood gases were pCO_2 42 mm of mercury, pH 7.38 and pO_2 59 mm of mercury.

A working diagnosis of tricyclic overdosage

From the Department of Medicine, University of California, Davis, School of Medicine and the Sacramento Medical Center.

Submitted February 14, 1972.

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was made. As the temperature fell toward normal the blood pressure dropped from 120/80 to 70/30 mm of mercury. Despite the administration of five liters of fluid, shock persisted, and norepinephrine drip was cautiously started.

The patient was transferred to intensive care where her blood pressure stabilized and she gradually became responsive. She had no seizure activity during her course. Digoxin 0.25 mg and furosemide (Lasix®) 40 mg were given intravenously to support cardiac function and augment urine output. It was soon learned that she had taken 30 tablets of tranylcypromine over the preceding three weeks in addition to five desipramine tablets the past six days. A gas chromatography screening, including salicylates, was negative; two blood cultures were negative and tests of thyroid function were all normal. Creatinine phosphokinase, lactic dehydrogenase, and serum glutamic oxaloacetic transaminase were all elevated but rapidly fell toward normal.

The clinical syndrome could be explained entirely by the interaction between the tranylcypromine and desipramine. The patient improved rapidly except for a few involuntary muscle twitches that also disappeared. Psychiatric consultants believed no brain damage had been done by hyperpyrexia and agreed to observe her as an outpatient upon discharge one week later.

Discussion

The combination of a tricyclic and a monoamine oxidase inhibitor may produce symptoms of dizziness, headache, nausea, vomiting, hyperexcitation, muscle spasm, convulsions, decerebrate rigidity, severe hyperpyrexia, bizarre behavior, and hypo- or hypertension with pronounced individual variation in sensitivity to the combination.[1,3] The severity of the situation must be stressed, since death is not a rare eventuality. Monoamine oxidase inhibitors are thought to produce irreversible inhibition of the enzyme; hence, it is necessary to allow two weeks after cessation of the drug for monoamine oxidase to reaccumulate before administering a drug with a potential interaction.[2] The mechanism of action of Norpramin® (desipramine hydrochloride), a rapidly-acting tricyclic, and of its interaction with a monoamine oxidase inhibitor is unknown. The most common adverse effect seen with the monoamine oxidase inhibitors is the hypertensive crisis in which an indirectly-acting amine (for example, tyramine in certain cheeses) is ingested, this causing acute elevation of blood pressure due to an exaggerated norepinephrine release.[2]

In 1964 tranylcypromine sulfate (Parnate) was temporarily removed from the market because of associated headache, increased blood pressure, and cerebrovascular accidents. An estimated three and a half million persons had taken the drug. In recent years it has been replaced by the tricyclic antidepressants. Monoamine oxidase inhibitors continue in use. For example, phenelzine sulfate (Nardil®) recently was used to suppress rapid eye movement sleep in treating intractable narcolepsy.[4]

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Refer to: Rahbari H: Congenital absence of pectoral muscles. Calif Med 117:66-68, Dec 1972

Congenital Absence of Pectoral Muscles

HOMAYOON RAHBARI, M.D.,
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THE ABSENCE OF pectoralis major muscle is probably the most innocuous cause of unilateral hyper-radiolucent lung (Table 1). A recent case of unilateral hyperradiolucent lung proved to be due to this congenital absence.

Report of a Case

The patient was a short, stocky, 30-year-old Caucasian man who was in hospital for acute psychiatric treatment. On a routine chest roentgenogram the radiologist noted left unilateral

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Submitted January 21, 1972.

From the Department of Internal Medicine, Kern General Hospital, Bakersfield, Ca.

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TABLE 1.—*Causes of Unilateral Hyper-radiolucence of Lung Field*

- A. Extrinsic
  - 1. Congenital
    - a) Absence of pectoral muscles
    - b) Sprengel's Deformity
    - c) Congenital scoliosis
  - 2. Acquired
    - a) Chest muscles deformity
      - 1) Atrophy due to disease or disuse
      - 2) Absence due to surgical excision
    - b) Acquired scoliosis
- B. Intrinsic
  - 1. Congenital
    - a) Unilateral congenital emphysema
    - b) Agenesis or hypoplasia of a pulmonary artery
    - c) Agenesis or hypoplasia of lobes of a lung
  - 2. Acquired
    - a) Unilateral emphysema
    - b) Thrombosis or embolism of a pulmonary artery
    - c) Swyer-James Syndrome*
    - d) Unilateral pneumothorax

---

*A syndrome of uncertain cause thought to be secondary to repeated unilateral lung infections resulting in obliterative bronchitis and bronchiolitis. Collateral ventilation develops distal to the obliteration resulting in secondary overdistention and emphysema. Synonyms: Bronchiolitis obliterans associated with transradiancy, chronic obstructive pseudoemphysema, idiopathic unilateral hyperlucent lung, unilateral hyperlucency of the lung, unilateral nonfunctioning lung. (Swyer PR, James GC: A case of unilateral pulmonary emphysema. Thorax, 1953, 8:133-136)

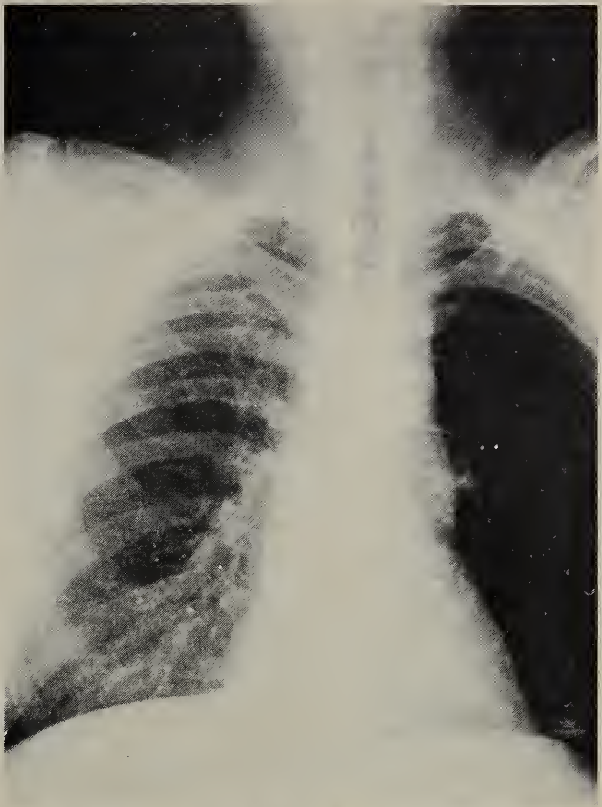

Figure 1.—Hyper-radiolucence on left, found to be due to congenital absence of pectoral muscles.

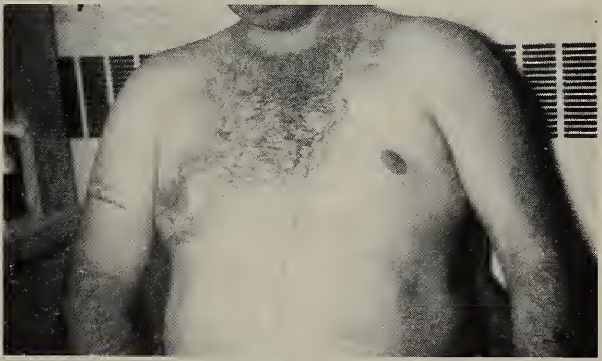

Figure 2.—Differences in hair growth and nipple placement due to absence of pectoral muscles on left side.

hyper-radiolucence (Figure 1). The patient had had a left forearm fracture in childhood with no adverse sequelae. He had been working as a construction worker, and gave negative family history regarding the body-build abnormality. The left side of the chest and the left shoulder and upper extremity appeared somewhat smaller than the counterparts (Figure 2). The left side of the chest was almost devoid of hair and perspiration, whereas the right side showed perspiration and considerable hair growth. The left breast was flat and the left nipple was placed more cephalad and laterally than the right. The respiratory and cardiovascular systems appeared normal. After having performed the appropriate maneuvers to decide the extent of the absence of the pectoral muscles (see discussion) it was concluded that this patient had congenital absence of about four-fifths of the pectoralis major and the complete absence of the pectoralis minor on the left side, together with hypoplasia of the left breast and partial absence of the skin appendages on the same side. (See Table 2.)

Discussion

Absence of pectoralis major and minor is not a frequent occurrence, but congenital variations occur more frequently in the pectorals than in any other of the skeletal muscles.[1] Often, as in this case, it is the pectoralis minor and the sternocostalis portion of pectoralis major which are missing.[2] The pectoralis major has two origins, the clavicular head and the sternocostal head. Both fleshy heads bend to form a tendon which turns on itself and inserts into the lateral wall of the bicipital groove of the humerus.[3]

TABLE 2.—*Anomalies Associated with Congenital Absence of Pectoral Muscles*

Ipsilateral digital anomalies[2,5,6,7]
Ipsilateral upper extremity shortening[5,6,7]
Absence or hypoplasia of the breast[1,5,6]
Deficiency of chest and axillary hair and sweat glands[1,5]
Defective ribs, costal cartilages, intercostal and shoulder muscles[1,5,6,7]
Scoliosis[6,7]
Sprengel's Deformity[6,7]

Bilateral absence of pectoral muscles, isolated absence of the clavicular portion of pectoralis major, or absence of pectoralis minor in the presence of pectoralis major are rarities.[1] There appears to be no dominance of pectoralis defects on either the right or the left side.[4]

Whether the absence of the pectoral muscles is determined genetically has not been answered clearly; if genetic determination is the case, the gene must be recessive and manifest itself rarely.[5] The embryologic pathosis of this deformity is best explained by faulty development of part of the upper limb bud.[6] Three possibilities have been suggested regarding the congenital absence of pectoral muscles:[1]

1. These structures fail to develop in the embryo.
2. The muscles develop partially, fail to attach to the bone, and subsequently atrophy.
3. The premuscle mass, which in normal development goes to form the pectoralis minor and two portions of the pectoralis major, fails to differentiate into its separate parts.

In an embryo of about 10.5 mm, lateral to the anterior six ribs lies the lateral premuscle mass. The fourth division of this premuscle mass, the pectoral premuscle, passes ventrally to the brachial plexus and joins the arm premuscle sheath.[7] The migration ventro-caudally of this pectoral premuscle mass influences the overlying portions of the skin. In the event of no migration, the mammary gland locates at a higher level and more laterally.[1] It is significant that in the present case the patient could engage in heavy manual labor without any difficulty. It has been noted that those of the living subjects who were in good physical condition showed no inconvenience or awkwardness because of the muscular deficiency.[1] The absence of pectoralis muscles in most cases can be diagnosed clinically. Katz[3] gives the following directions: The subject holds his arms forward a little below the horizontal, and with elbows extended he presses his palms strongly together. This brings the whole muscle into vigorous action, and the two parts, as well as the tendon, can be plainly seen and felt. Then, while the subject is doing this, the observer presses down on the extended arms and instructs the subject to resist the pressure. This instantly causes relaxation of the lower half while the upper half stands out in still stronger action. Conversely, if the observer lifts against the arms and the subject resists, then the upper half relaxes and the lower half acts.

Conclusion

Unilateral hyper-radiolucence of the lung on a roentgenogram merits extensive investigation. One of the simplest reasons for the anomaly is the congenital absence of pectoral muscles.

Summary

The congenital absence of pectoralis minor and sternocostalis portion of pectoralis major on one side is one of the causes of unilateral hyper-radiolucent lung. One suggested mechanism for the congenital absence of the pectoral muscles is the failure of the differentiated parts of the pectoral pre-muscle mass in the embryo to become attached to their ultimate insertion sites, and consequently lead to atrophy.

This anomaly can be easily diagnosed clinically by appropriate checks for the function of these muscles.

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Refer to: Lewis JE, Sheptin C: Mycoplasmal pneumonia associated with abscess of the lung. Calif Med 117:69-72, Dec 1972

Mycoplasmal Pneumonia Associated With Abscess Of the Lung

JAMES E. LEWIS, M.D., AND
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THE RADIOLOGIC CHANGES in mycoplasmal pneumonia are well documented.[1-5] The infiltrate is usually unilateral and involves one or more segments of a single lobe, usually one of the lower lobes. A soft, patchy, localized bronchopneumonia is usually seen which frequently fans out from the hilus of the lung. Occasionally, a mottled, reticular or disseminated pneumonia is seen; lobar pneumonia is uncommon. Pleural effusions are generally infrequent and small,[5,7-9] although massive effusions have been reported.[5,6] A review of the literature failed to reveal any case of documented lung abscess in an uncomplicated case of mycoplasmal pneumonia.

Report of a Case

The patient, a 24-year-old Caucasian auto body shop worker, presented with a two-week history of sore throat followed by substernal and anterolateral chest pain. The patient produced copious amounts of green, mucoid, non-fetid sputum that was occasionally blood-tinged. Symptoms were intermittent but progressive with headache, chills, diaphoresis, malaise and myalgias. He had lived in Bakersfield, California, in the past years but denied contact with tuberculosis or pathogenic inhalants except for the smoking of one pack of cigarettes a day. He consumed 12 to 24 ounces of beer a day and was allergic to penicillin.

On examination at Santa Clara Valley Medical Center on October 3, 1970, his temperature was 99.4°F., blood pressure 112/78 mm of mercury, pulse rate 96, and respiration rate 24. His pharynx was mildly erythematous but without exudate. He had moderate respiratory distress and bilateral splinting on inspiration but no dyspnea or cyanosis. Dullness and decreased breath sounds were noted over the base of the left lung posteriorly, with occasional fine moist rales.

The roentgenologic examination of the chest on admission revealed a homogeneous infiltrate in the superior division of the lingular segment (Figure 1). In the lateral aspect of the lingula there was an air-fluid level consistent with pulmonary cavitation. Four days later the effusion had progressed (Figure 2). Following pleural biopsy with the Abrams needle, 450 ml of serosanguinous fluid was removed. Before the biopsy the fluid was serous. Analysis of the fluid showed a total protein of 5.4 gm per 100 ml, a red blood cell count of 6,000, neutrophils 2,400 and mononuclear cells 2,400 per cu mm. Aerobic and anaerobic cultures of the pleural fluid were negative for bacteria, acid-fast organisms and fungi.

Leukocytes numbered 10,800 per cu mm, with 84 percent neutrophils, 12 percent lymphocytes, 3 percent monocytes, and 1 percent eosinophils. The hematocrit was within normal limits. Screening chemical panel 16 was normal except for serum albumin of 2.9 gm per 100 ml and glutamic oxaloacetic acid transaminase 110 mμ per ml (normal 10 to 50). Immunodiffusion of the patient's serum revealed an immunoglobulin A (IgA) level of 408 mg per 100 ml (normal 90 to 274 mg), IgG of 1500 mg (normal 737-1481) and IgM of 160 mg (normal 40-128).

A Gram stain of the sputum showed a few pus cells and rare Gram-positive cocci and Gram-negative rods. Aerobic cultures of deep productive sputum before the administration of antibiotics and twice during the treatment with cephalosporins grew saprophytic neisseria, alpha hemolytic streptococci, hemophilus species, gamma hemolytic streptococci, diptheroids, and rare yeast colonies. Specific anaerobic cultures of the sputum were not obtained. Three sputum cultures for fungi showed no growth and three paired cultures of the blood for aerobic and anaerobic organisms were negative.

A coccidioidin skin test (1:100) was positive (20 mm induration at 72 hours), but complement fixation and precipitin antibody titers for coccidiomycosis were negative.* The tuberculin skin test (intermediate strength of purified protein

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From the Department of Medicine, Santa Clara Valley Medical Center, San Jose.

Submitted February 28, 1972.

Reprint requests to J. E. Lewis, M.D., Department of Medicine, Santa Clara Valley Medical Center, 751 S. Bascom Avenue, San Jose, Ca. 95128.

*Performed by the laboratories of Dr. D. Pappagianis, University of California, Davis, School of Medicine, Davis, California.

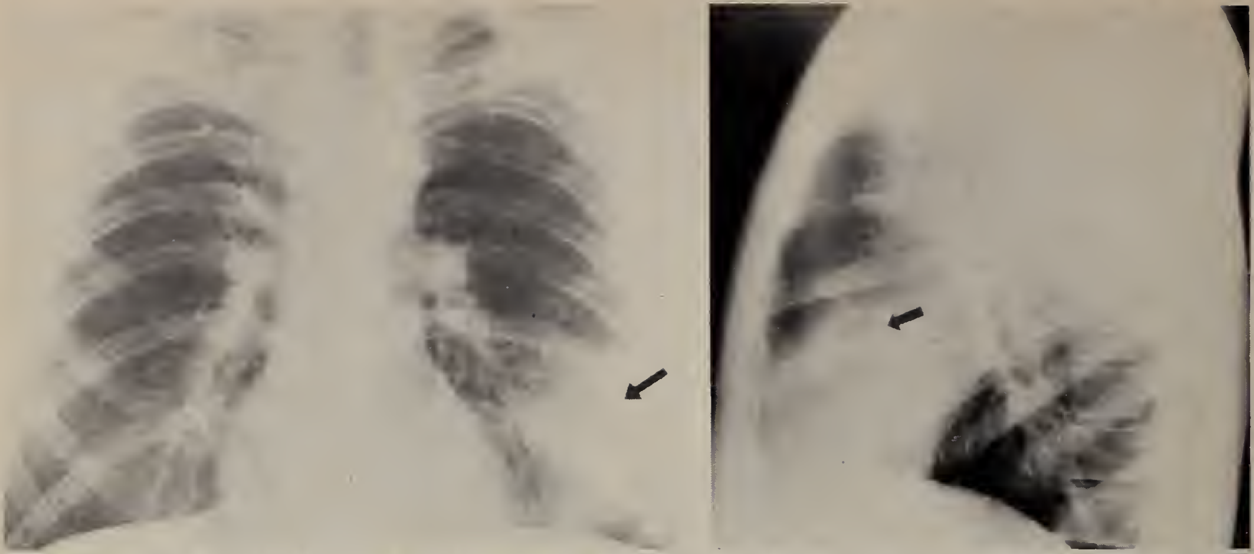

Figure 1.—*Left,* admission posterior-anterior chest x-ray film taken October 3, 1970 shows lingular infiltrate with air fluid level in the lateral portion consistent with cavitation. Peribronchial infiltrate seen in the right lower lobe. *Right,* lateral view demonstrates cavitation and associated fluid in the major fissure.

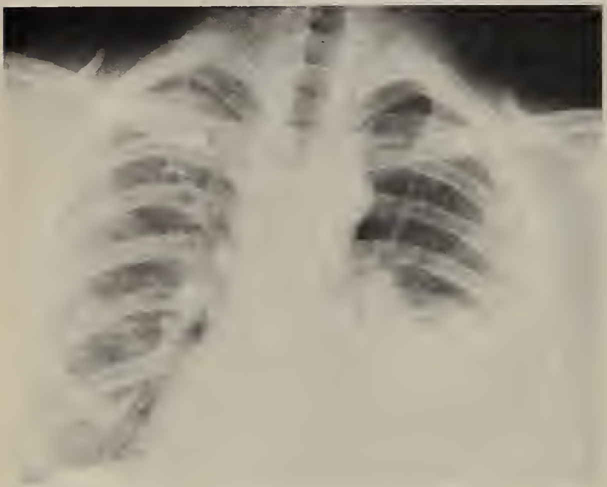

Figure 2.—Film taken October 7, 1970, shows massive left pleural effusion and left lower lobe infiltrate obscuring the cavity.

derivative) was normal and sputum smears and cultures for acid-fast bacilli were negative.

Complement fixation titers** were initially less than 1:8 for influenza A, influenza B, adenovirus and Q fever. Psittacosis-lymphogranuloma venereum titer was 1:8 ("indicating infection at some time") and the titer of complement fixation antibody for mycoplasma pneumoniae was 1:1024. Titers during convalescence obtained three weeks later and performed simultaneously were unchanged except for Mycoplasma pneumoniae which had decreased to a 1:8 titer. During this time interval a rise in cold agglutinin titers from less than 1:4 to 1:32 was noted.

The patient's fever, chest pain, productive cough and radiologic changes were unimproved after four days of treatment with cephalothin, 3 grams intravenously every six hours. On the fifth day, because of local venous tenderness, therapy was changed to cephaloridine, 1 gm intravenously every six hours. The pulse rate varied from 80 to 100, the respiratory rate from 18 to 26, and the oral temperature remained at 101°F. The lack of clinical response and the suspicion of mycoplasmal pneumonia led to the administration of tetracycline by mouth, 500 mg every six hours. Over the next 96 hours the patient became afebrile and improved clinically. By the sixteenth hospital day the chest x-ray showed resolution of the pleural fluid and parenchymal infiltrate. A small cavity was still present. Six weeks after admission a chest x-ray film revealed only minimal lingular scarring.

Comment

Diagnostic criteria for mycoplasmal pneumonia include: (a) isolation of Mycoplasma pneumoniae, (b) a four-fold rise in the convalescent titer of complement fixation antibody[1,5,9-11] or (c) a single complement fixation titer variously reported as greater than 1:32 to 1:256.[1,9,10] Although specific attempts at isolation of Mycoplasma

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**Performed by the California State Department of Public Health, Berkeley, with the use of Microtiter Complement Fixation Test with "raw" and "lipid" antigen as described by Purcell RH, Chanock RM *In* Diagnostic Procedures for Viral and Rickettsial Infections, Ed Rennett, NJ Schmidt, eds, Chapter 23, American Public Health Association, Inc., New York, 1969, p. 814.

pneumonia were not carried out, the patient's initial titer for complement fixation antibody of 1:1024 three weeks after the onset of symptoms meets the most rigid criterion of the last standard, and indeed is one of the highest recorded in all of the above series. A four-fold rise in cold agglutinin titer,[3,4,10,12,13] as occurred in our patient, is considered strongly supportive of a diagnosis of Mycoplasma pneumoniae infection.

The association of Mycoplasma pneumoniae with lung abscess has not been previously documented. George et al[5,13] commented upon four patients who had "pneumatoceles" that cleared quickly. In the radiographs published by those observers the "pneumatoceles" (although admittedly not well seen) appeared to be outside the area of incomplete segmental consolidation and did not contain any fluid. In all probability they really were pneumatoceles and not true abscesses of the lung. In their series of 500 patients in 1951 with "primary atypical pneumonia," Robertson and Morle[8] mentioned two cases of abscess formation within the pulmonary infiltrate. Unfortunately, detailed bacteriologic study was not undertaken and no mention of cold agglutinin titers in the two patients was made. At that time, complement fixation titers for Mycoplasma pneumoniae were not available. Because of these reservations, the exact nature of the illness in the two patients with lung abscess is uncertain.

Pleural effusions, although infrequent, have been reported in association with mycoplasmal pneumonia.[5,7-9] Massive pleural effusions, as was present in the case reported, are distinctly rare.[5,6] Our patient's elevated pleural fluid protein and the mixed numbers of leukocytes and red blood cells are similar to those reported in other effusions associated with mycoplasmal pneumonia,[4,9] although the fluid for analysis was taken after the biopsy in the present case, making more detailed interpretation difficult. The pleural biopsy showed no evidence of granulomatous disease.

The positive coccidioidin skin test with negative complement fixation and precipitin antibody titers three weeks after the onset of symptoms is attributed to previous habitation in an endemic area with probable subclinical infection. The low positive Psittacosis-lymphogranuloma venerum titer was the same in acute and convalescent sera and may be attributed to previous subclinical infection. The elevations of the IgA, IgG, and IgM are nonspecific but are compatible with those previously described in Mycoplasma pneumoniae infections.[14]

The modest leukocytes without left shift, especially in view of the extensive pulmonary involvement and effusion, might favor viral rather than bacterial cause. A primary abscess of the lung cannot be excluded completely in our patient, because it would have a similar clinical course and defervescence as that of our patient, and specific anaerobic cultures of the sputum were not obtained. However, the absence of fetid breath and of musty odor to the sputum, of periods of unconsciousness, and of emesis or trauma are evidence against a primary abscess of the lung. The relatively rapid resolution of the cavity makes the diagnosis of a pre-existing cavity, cyst, or bleb with superimposed Mycoplasma pneumoniae infection unlikely. We cannot with certainty exclude some other primary pulmonary disorder that might predispose to the development of mycoplasmal infections. Our patient clearly had a mycoplasmal pneumonia with a definite cavity that contained fluid. The nonbacterial nature of the illness was further substantiated by failure to isolate pathogenic bacteria despite multiple cultures of the sputum, blood, and pleural fluid and gradual clinical and radiographic worsening in spite of intensive antibiotic therapy with the cephalosporins. The clearing of the pneumonia and abscess both clinically and radiographically, after the addition of tetracycline therapy, is also compatible with the well documented sensitivity of Mycoplasma pneumoniae to tetracycline.[13,15,16]

Summary

A previously undescribed complication of mycoplasmal pneumonia, the formation of a pulmonary abscess, is reported in one patient. The complement fixation titer for Mycoplasma pneumoniae was positive at 1:1024 and a four-fold rise in cold agglutinin titer was observed. All bacteriologic studies were normal. On radiologic examination a lingular infiltrate with an air-fluid level consistent with cavitation was demonstrated. Massive pleural effusion developed before the gradual resolution of both processes. Perhaps more careful study of patients with "primary abscess" of the lung may reveal additional cases of mycoplasmal pneumonia associated with lung abscess.

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Refer to: Knodell RG, Kirsch E, Rygg GC: Fascioliasis—Response to bithionol. Calif Med 117:72-74, Dec 1972

Fascioliasis

Response to Bithionol

Robert G. Knodell, M.D.,
Edward Kirsch, M.D., and
George C. Rygg, M.D., *San Francisco*

FASCIOLA HEPATICA is an increasingly important parasite of man in Latin American and Mediterranean countries. Although the organism is enzootic in extensive areas of the southern, southwestern, and western United States,[1] only six cases of human fascioliasis have been reported in this country.[1-5] The course of this disease is characterized by clinical manifestations for up to three months before the diagnostic appearance of ova in the stools. Our report illustrates the clinical features which should arouse suspicion of fascioliasis and describes the clinical course and changes in serial liver scans during therapy with bithionol.*

Report of a Case

A 55-year-old Mexican-American man was admitted to another hospital in April 1971. He had had constant right upper quadrant pain, occasional diarrhea, malaise, and fever of one week's duration. He and his family had returned from a one-month vacation in Mexico in February. Physical examination revealed tender hepatomegaly. There was no splenic enlargement, friction rub, or rebound abdominal tenderness. Leukocytes numbered 24,000 per cu mm with 64 percent eosinophils. Progressive weight loss and daily spiking fevers to 39.8°C (103.5°F) persisted for four weeks despite extensive diagnostic tests that included ten negative examinations for ova and parasites in the stool and a trial of metronidazole.

The patient was transferred to the University of California Hospital in San Francisco. Hemoglobin was 8.7 grams per 100 ml, the hematocrit 26 percent, and leukocyte count 15,900 per cu mm with 68 percent eosinophils. The erythrocyte sedimentation rate was 108 mm in one hour. Total iron-binding capacity was 146 mg per 100 ml with 50 percent saturation. The vitamin B_{12} level was 520 picograms per 100 ml. Coombs tests were negative. Bone marrow showed mature eosinophilic hyperplasia with normal iron stores and no granulomas or evidence of metastatic malignant disease or leukemia. Liver function tests yielded the following abnormal values: alkaline phosphatase, 252 international units (IU) per liter (normal, 25 to 80 per liter); and leucine aminopeptidase, 105 IU per liter (normal, up to 45 per liter). Bilirubin, glutamic oxaloacetic transaminase, and lactate dehydrogenase were normal. Skin tests for fungal diseases and tuberculosis were negative, as were serological tests for infection due to Entamoeba and Echinococcus. An upper gastrointestinal series and barium enema studies were negative. A cholecystogram and a cholangiogram showed no calculi and no dilatation of the biliary system.

Multiple focal defects were seen on liver scan

From the Department of Medicine, School of Medicine, University of California, San Francisco.

Submitted February 29, 1972.

Reprint requests to: Editorial Office, 998-M, Department of Medicine, University of California, San Francisco, Ca. 94122.

*Experimental drug provided by the Parasitic Disease Drug Service, Parasitic Diseases Branch, Epidemiology Program, Center for Disease Control, U.S. Public Health Service, Atlanta, Ga. 30333.

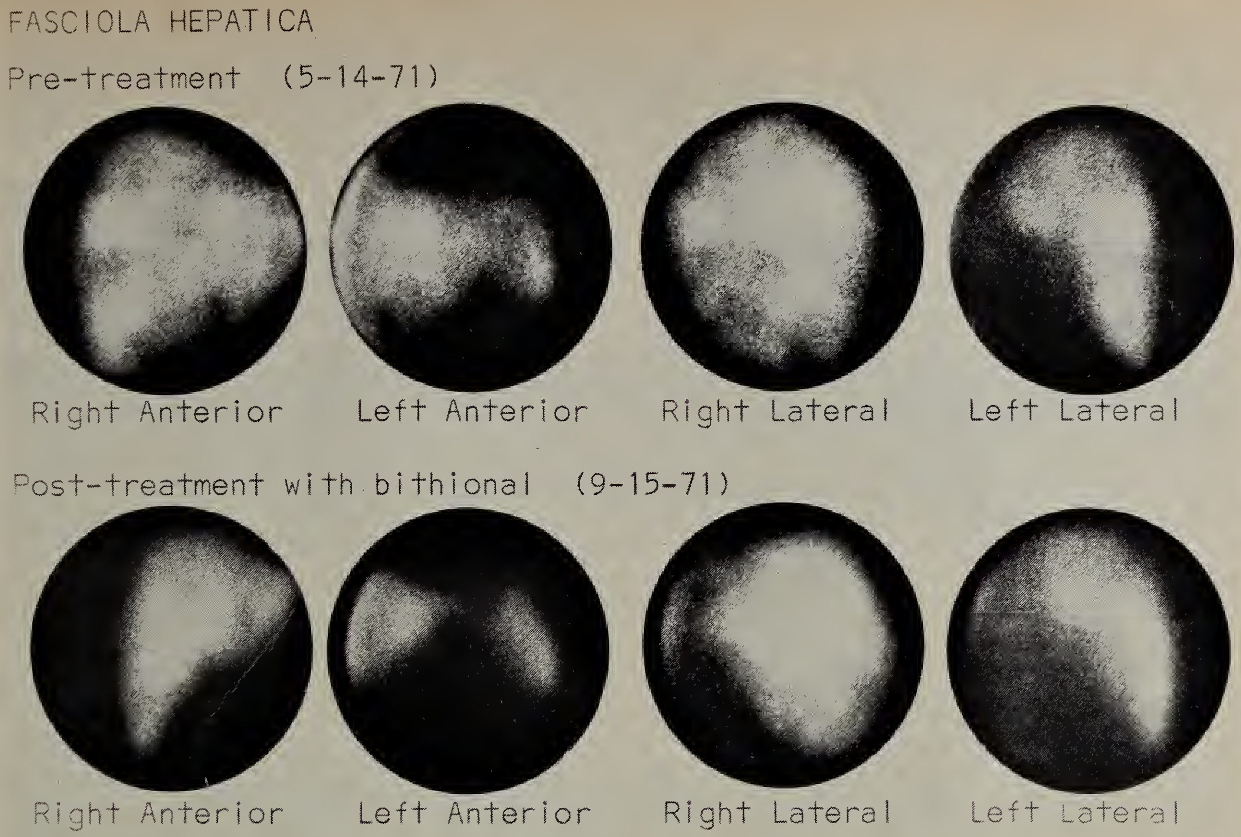

Figure 1.—Selected views of liver scans obtained before and eight weeks after treatment with bithionol.

(Figure 1). One week after admission and three and a half months after the patient's return from Mexico, examinations of stool became positive for ova of Fasciola hepatica (Figure 2). Immediately before treatment, quantitative egg counts were 37 eggs per gram of stool (formalin-ether concentration method of Richie performed on four 1-gram samples of stool). Bithionol, 50 mg per kg of body weight daily, divided into three oral doses, was given on alternate days to a total dose of 45 grams.[6] The patient experienced mild epigastric pain and one episode of vomiting, but no other side effects were noted. Two days after initiation of therapy he became afebrile, and after nine days of treatment ova were no longer seen in the stools. Multiple follow-up examinations for ova have been negative. The patient has regained 14 of a 17-kilogram loss of weight during the illness, and has no gastrointestinal complaints. Hematocrit is 40 percent, leukocyte count 8,100 per cu mm with 14 percent eosinophils, and the erythrocyte sedimentation rate 33 mm in one hour. Results of liver function tests are normal. Liver scan shows mild hepatomegaly with pronounced improvement in the labeling defects noted initially (Figure 1).

Discussion

Sheep are the major definitive host of Fasciola hepatica; man is an accidental host. Eggs passed in feces of sheep and other herbivores hatch miracidia which invade and develop within snails of the genus Lymnaea. Mature cercariae are released and encyst on waterside plants. (The patient and his family ate the same foods while in Mexico, except that he alone used watercress in his iced tea.) Once ingested, metacercariae excyst and migrate through the intestinal wall, penetrate Glisson's capsule, and migrate through hepatic parenchyma to the biliary passages, where they mature. Adult worms provoke inflammation and adenomatous changes of the biliary epithelium with surrounding fibrosis.[7] If the process continues, pressure atrophy of the liver parenchyma and periportal fibrosis may occur. Cramping right upper quadrant pain, fever, and eosinophilic leukocytosis are a common presenting triad. Other symptoms include anorexia, weight loss, vomiting, diarrhea, cough, pruritis, and urticaria. Symptoms are often present for six weeks or more before the appearance of ova in the feces, and the minimum interval between

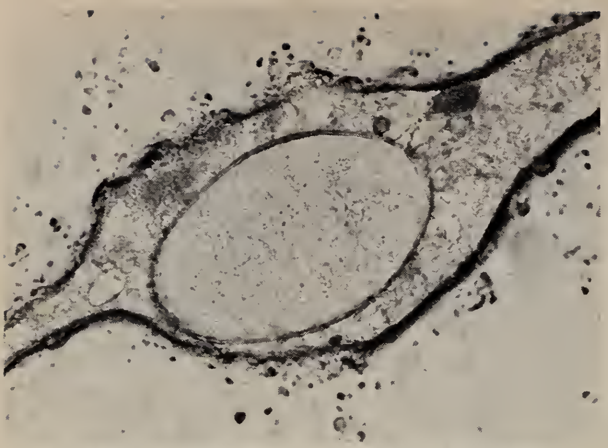

Figure 2.—Typical ovum of Fasciola hepatica.

ingestion of the larvae and the appearance of ova in feces is three months.[8]

Emetine has been the mainstay of therapy in the treatment of fascioliasis. The incidence of adverse side effects is high, diarrhea, nausea and vomiting occurring in 30 to 50 percent of patients.[9] Cardiovascular effects, such as hypotension, tachycardia and severe precordial chest pain, may necessitate discontinuation of therapy.[10] Bithionol has only recently been used in the treatment of fascioliasis.[6,11] Diarrhea, vomiting, abdominal pain and urticaria are its most frequent side effects.[12] Cardiovascular effects are rare,[13] and changes in renal, liver or hematologic function have not been reported.

Human fascioliasis may mimic acute hepatitis, cholecystitis or intrahepatic malignant disease. However, a carefully taken history, with special attention to ingestion of aquatic plants, and a clinical picture of right upper quadrant pain, fever and eosinophilic leukocytosis should enable presumptive diagnosis. Complement-fixation tests have been developed that are positive before ova appear in the stool,[6,14] but such tests were not available for use with this patient. Diagnostic ova will not be passed in feces for as long as six weeks after the onset of clinical illness; therefore, negative results of stool obtained before this interval should not prevent re-examination. Tenacity and a high degree of suspicion should lead to early diagnosis and therapy before irreparable liver damage occurs.

ACKNOWLEDGEMENT: Dr. Malcolm R. Powell, Department of Radiology, performed the liver scans.

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DIARRHEA IN THE MORNING? IT'S PROBABLY "FUNCTIONAL"

A functional gastrointestinal disturbance is the most likely diagnosis in the patient who comes in complaining of early morning diarrhea. He may not tell you that it is early morning diarrhea; but as you pin him down about the timing, you will find that he is out of bed early in the morning. Sometimes before the alarm goes off, he must get up and have a bowel evacuation. Then there will be a second before breakfast and a third right after breakfast. There will be a fourth before he goes to work; and then he is through for the day. Once you can identify that particular timing of a bowel habit, you can almost be certain that the patient has a functional gastrointestinal disturbance—an irritable, spastic bowel, an overactive bowel.

—H. Marvin Pollard, M.D., Ann Arbor

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In the Forefront

A New Community Health Care Center

The Our Lady of Guadalupe Facility in Daly City

Patricia Wright, *Daly City*

Early in 1971, after several tragic deaths, members of several community organizations joined together in an effort to bring primary health care services to their community. These organizations, representing Chicano-Latinos, Blacks, American Indians and Anglos, formed a unique multi-ethnic coalition which then approached Mary's Help Hospital, the San Mateo County Medical Society, the San Mateo County Board of Supervisors, the City of Daly City and other "provider" organizations to help them set up a neighborhood health center. The community made its plight known in a variety of ways—a pray-in on the lawn of Mary's Help Hospital, public appearances before the Board of Supervisors, press conferences, public discussions, and personal appeals. The people involved in the birth of the health center were of the community. They knew the deprivation and prejudices their people had suffered, and they were best able to make their needs known to and felt by the community at large.

Members of the various organizations involved in the genesis of the Guadalupe movement formed a board of directors and the clinic became a nonprofit corporation. Representatives of Mary's Help Hospital and other provider groups were added to the board, and also served as advisors. These providers gave some direct assistance to the clinic. The hospital donated some medical and dental equipment, the County of San Mateo agreed to pay two physicians' salaries, and the San Mateo County Medical Society provided consultation services. But there was still no operating capital. While volunteers began to register patients in a room made available by the hospital, the Board members began to seek the much needed operational money from the private sector. Soon $8,000 was secured through donations from two foundations and an individual donor.

With $8,000 in the bank and high hopes for the future, Our Lady of Guadalupe Health Center opened its doors July 1, 1971, in four small rooms above a real estate office on Mission Street in Daly City. In the first month, 71 families were registered, and 85 patients were seen by the two physicians.

As the months passed, the community clarified its goals and learned what it means to run a health center. It was agreed that the patients should receive quality care with the least amount of hassle. This meant that the intake process should be brief, avoiding as many personal or embarrassing questions as possible. It meant that anyone who walked through the door would be seen without first going through lengthy inquiry as to residence, income, and the like. During the first year, appointments were not necessary and, most important, the staff was friendly, understanding, and bi-lingual.

The non-medical staff, volunteer for the first few months, was composed of community peo-

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The author is Health Planner at Our Lady of Guadalupe Health Center.

Reprint requests to: Gene C. Taylor, Executive Director, San Mateo County Medical Society, 122 North El Camino Real, San Mateo, Ca. 94401.

ple who had been involved with the health center from its inception. Untrained in medical care administration or delivery, they made up in energy and improvisation what they lacked in background. Often working 16 or more hours a day, the three person staff managed not only to keep the clinic open but to make it progress. The number of people served by the clinic grew daily, with 138 families by the end of the second month and 267 by the end of the third month. In December, the City of Daly City allowed the health center to hire two more employees through Emergency Employment Act funds. A Regional Medical Program grant added a planner and part-time assistant in January. This staff was supplemented by volunteers, including professionals, students and community people.

By January it had become clear that the health center could not continue to operate at the current level and meet its expenses without generating income from somewhere. The County of San Mateo extended its aid through July, and several small private contributions were received. The clinic went through crisis after crisis, seldom able to pay the rent on time, often unable to pay staff. The only thing that seemed to keep the clinic open was the undaunted faith of the community that "Guadalupe will never close." And somehow, it never did.

The planning staff began to write grant applications for both federal and private funding. While many of the programs were special projects, each one would allow Guadalupe to either continue providing a current service or to expand services. Of the ten grants applied for, seven have already been funded, for a total of $368,163. The largest is an HEW Family Health Center developmental grant to investigate the feasibility of becoming a prepaid capitation program. This will serve to stabilize Guadalupe so that the board of directors can concentrate on making the health center self-supporting without losing sight of the need for sensitivity and concern for each patient. Because the board does not want to put itself into the position of having to turn people away, alternative payment mechanisms will have to be developed. But creativity is the essence of Guadalupe and this challenge will be met as have all others.

Guadalupe Health Center is a comprehensive health care center which is open from 7:00 p.m. to 10:00 p.m., Monday through Friday. It deals with the whole person, not just part of him. It currently provides mental health and social services as well as ambulatory care. With the assistance of students from the University of California, the health center is now in the process of setting up a complete dental unit. Health education, outreach, pharmaceutical services and expanded hours are anticipated for the future. The health center will soon move from the four crowded rooms to the two-story former City Hall building. In a unanimous action in late August, the City Council agreed to rent the building to the clinic at a price it could afford. A medical audit will be provided by the San Mateo County Medical Society to assure quality of care for all patients. This audit will also produce more of the types of data necessary to plan for the growth of the clinic. It is total community support of this kind which will insure the success of Guadalupe.

In one year, Guadalupe Health Center has grown from a small, inexperienced free clinic to a health care delivery system for the underserved population in Northern San Mateo County. Over 1200 families have now registered as Guadalupe patients. The two physicians treat approximately 400 patients monthly.

What makes Guadalupe different from other health centers? Why have providers rallied behind the clinic? Why has the California Medical Association recently voted a commendation for Guadalupe? Perhaps the answer lies in the people. The Guadalupe community *organized itself* around an issue which is very important in their lives—health care. The community did not allow someone to come in and tell it what it needed—or what outsiders thought was needed. The energy was generated from within and was directed from within. And this energy allowed the community to break through barriers which normally impede progress. The energy broke through the barrier of ethnic differences to allow all of the poor and all of the minority groups to work together for a common cause, rather than expending energy in conflict among themselves. The energy overcame barriers and there were free discussions and sharp debates with the established medical providers and others. But the energy was expended positively rather than negatively. The community said, "How will you help us?" rather than "Why haven't you helped us?"

The community was willing to first "go through channels" to get help, and it found that people were receptive. The energy broke through the bureaucratic barriers of the government as the community applied for grant after grant. While bureaucrats within the system were saying, "Guadalupe will never be considered for this program," Guadalupe was saying, "We not only will be considered, we will be chosen." And by channeling this positive energy in the right direction, Guadalupe has received incredible support. As Daly City's Mayor Bernard Lycett said as he was giving the clinic permission to rent the former City Hall building, "A year ago we didn't think you'd make it, but you have not only made it, you now have a whole building."

The heroes and heroines of the Guadalupe story are too numerous to name. Each board member has contributed significantly to the progress of the health center. Each patient has given us the reason and the energy to continue. Each staff person has given much more than could reasonably be expected of himself or herself. The provider community has stood always ready with technical assistance, material support, and genuine good will. As Guadalupe prepares to make the transition from a free clinic to a self-supporting primary health care delivery system, we will keep these contributions in mind so that we too will not become inaccessible or unacceptable to the population we are committed to serve.

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PUBLIC HEALTH REPORT

Frederick B. Hodges, M.D., Director, State Department of Public Health

Hazardous Waste Disposal

More than 70 million tons of solid wastes are produced each year in California as a result of domestic, industrial and agricultural activities. Hazardous waste represents only a small fraction of the total solid waste production, but it presents serious public health and environmental problems, alleviation of which often requires special handling and disposal procedures and techniques.

Hazardous materials include, among other things, some medical, chemical and industrial wastes and explosives, used pesticide containers and radioactive wastes. Wastes may be solid, semi-solid, or liquid, and they represent various levels of danger because they are toxic, infectious, irritant, corrosive, explosive, flammable, radioactive or strong sensitizers.

Handling procedures expose workers to such materials by direct contact or inhalation; for instance, they may handle aqueous industrial wastes or breathe vapors from evaporating solvents such as used cleaning solutions. Disposal equipment operators have been hospitalized after handling toxic chemicals or crushing containers filled with explosive chemicals. Personnel at disposal sites often do not know the content of such containers or the toxic nature of the materials in them.

Hospitals and medical and veterinary clinics generate many hazardous wastes which must be discarded safely, including infectious materials, sharp medical instruments, needles, syringes and drugs. Refuse collectors come into contact with infectious wastes when servicing medical facilities, or they may receive cuts or punctures from some of these objects. The public is endangered if these are thrown into an open dump where access is unrestricted and scavengers can handle them.

Under the California Administrative Code, certain kinds, quantities and concentrations of radioactive waste may be released into sanitary sewerage systems. Radioactive waste packaged in accordance with regulations of the U.S. Department of Transportation may be transferred to licensees authorized to receive it. It is then taken to authorized land burial sites for burial. At present there is no authorized site in California, the nearest one being in Nevada.

The State Health Department is one of several federal, state and local agencies sharing responsibilities for the management of hazardous waste in California, protecting workers in industry and at disposal sites, and safeguarding the general public. In studying solid waste management planning efforts, the Department learned that hazardous wastes in some instances are being disposed of in a manner which creates public health and environmental problems. It was also apparent that technological improvements and standardization of procedures were needed.

Altogether, there are about 700 general use disposal sites in California. A small number are designated as suitable for disposal of hazardous wastes, and they are set up to take industrial sludges, slurries and spent liquids, thus receiving most of the hazardous waste produced. Some sites will accept only industrial wastes. Others accept a combination of general solid wastes and industrial wastes. Other dangerous wastes are disposed of in conjunction with industrial waste processing facilities and in on-site disposal areas of certain industrial plants. Because there are not enough industrial waste disposal sites in the state, some general refuse sites take limited quantities of unauthorized industrial chemical wastes. There has not been enough time, money or manpower available to monitor the sites.

Thermal decontamination by incineration and autoclaving is used to process most infectious materials and wastes. The California Administrative Code requires that infectious wastes from hospitals be incinerated or disposed of as directed by the local health officer and most such materials are destroyed by on-site incineration. It is known that on occasions when incineration equipment becomes overloaded or fails to work properly, such materials are sometimes brought to the local general refuse disposal site, often without knowledge of the site operator. Another problem is that few incinerators currently on the market can economically process medical wastes yet comply with air pollution control regulations. The increasing amount of plastic disposables in hospital waste and the increasingly restrictive air pollution regulations have compounded the problem. More stringent regulations for the temporary storage of infectious wastes in hospitals and nursing homes are now under consideration.

A recent law (AB 254) amended the Health and Safety Code to authorize destruction of hypodermic syringes and needles by grinding and disposal in sewerage systems where such disposal is authorized by the agency with jurisdiction over the system. It also permits infectious wastes (defined as any material or article which may have been exposed to contagious or infectious disease), human tissues or recognizable anatomical human remains to be disposed of by interment, incineration or any other method which the State Health Department determines to protect the public health, instead of requiring as in the past that disposition be by interment or incineration only.

Storage and disposal of hazardous wastes from physicians' offices present the same problems as those in hospitals and nursing homes. Physicians may store wastes in garbage cans. If they are not tightly closed, flies may transmit disease organisms by contact with infectious wastes. Animals may overturn cans and scatter their contents. Children are sometimes attracted to needles, syringes, and other hazardous wastes. Refuse collectors have reported that overloaded waste cans tend to spill, so that they must handle infectious hazardous materials.

The Department, therefore, urges that physicians break or otherwise render unusable all needles and syringes before disposal and that they put infectious and other medical wastes in plastic bags which can be tied securely. If possible, bags awaiting collection should be stored in a locked container. Wastes that cannot safely be flushed to the sewer should be taken to a sanitary landfill rather than to an open dump.

The Department recommends a thorough physical examination of new employees at hazardous waste disposal facilities, with periodic medical check-ups thereafter. The physician should be alerted regarding the kinds of materials to which an employee may have been exposed so that appropriate diagnostic procedures can be undertaken for occupational diseases. Under California law, physicians are required to report cases of occupational diseases or injuries.

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Information

Selected Item from the FDA Drug Bulletin

Use of Drugs for Unapproved Indications: Legal Responsibility

■ *The widespread use of certain prescription drugs for conditions not named in the official labeling has led to questions concerning the legal responsibilities of prescribing physicians, and the position of the Food and Drug Administration with respect to such use.*

FDA is proposing a regulation clarifying the legal status of the package insert and specifying actions that may be taken by FDA with respect to unapproved uses of approved prescription drugs.

THE MAJOR OBJECTIVE of the drug provisions of the Federal Food, Drug, and Cosmetic Act is to assure that drugs will be safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling.

When a new drug is approved for marketing, the conditions of use that have been approved are required to be set forth in detail in the official labeling. This labeling must accompany the drug in interstate shipment and must contain adequate information for safe and effective use of the drug, including indications, effects, dosages, routes, methods, and frequency and duration of administration, contraindications, side effects, and precautions.

The labeling is derived from the data submitted with the new drug application. It presents a full disclosure summarization of drug use information which the supplier of the drug is required to develop from accumulated clinical experience and systematic drug trials consisting of preclinical investigations and adequate well-controlled clinical investigations that demonstrate the drug's safety and the effectiveness it is represented to possess.

The requirements of the law are satisfied when an approved new drug is shipped in interstate commerce with the approved package insert, and neither the shipper nor the recipient intends that it be used for an unapproved purpose. Once the new drug is in a pharmacy, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining approval of the Food and Drug Administration.

This interpretation of the law is consistent with congressional intent as indicated in the legislative history of the Food, Drug, and Cosmetic Act. Congress did not intend the Food and Drug Administration to interfere with medical practice. Congress recognized a patient's right to seek civil damages in the courts if there should be evidence of malpractice, and declined to provide any legislative restrictions upon the medical profession.

However, Congress clearly required FDA to control the availability of drugs for prescribing by physicians. Under the 1938 Food, Drug, and Cosmetic Act, a new drug could not be marketed unless a New-Drug Application establishing the drug's safety had been approved by FDA. Under the 1962 Amendments, no new drug is permitted on the market until FDA approves a new-drug application demonstrating both its safety and effectiveness.

Under the 1962 Amendments, moreover, FDA is required to review the labeling for every new drug, including the package insert for prescription new drugs, and to approve it as not false or misleading in any particular. In approving the labeling FDA must determine that the content is entirely truthful, and that it omits no information pertinent to the safe and effective prescribing of the drug by the physician. Congress intended the labeling to be a full, complete, honest, and accurate appraisal of the important facts that have reliably been proved about the drug.

Thus, although it is clear that Congress did not intend FDA to regulate or interfere with the practice of medicine, it is equally clear that it did intend FDA to determine those drugs for which substantial evidence of safety and effectiveness exists and thus will be available for prescribing by the medical profession, and additionally, what information about the drugs constitutes truthful, accurate, and full disclosure to permit safe and effective prescription by the physician.

As the law now stands, therefore, FDA is charged with the responsibility for judging the safety and effectiveness of drugs and the truthfulness of their labeling. The physician is then responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling and other data available to him.

Although the law does not require a physician to file an investigational new drug plan before prescribing an approved drug for unapproved uses, or to submit to FDA data concerning the therapeutic results and the adverse reactions obtained, it is sometimes in the best interests of the physician and the public that this be done.

The physician should recognize that such use is investigational, and he should take account of the scientific principles, including the moral and ethical considerations, applicable to the safe use of investigational drugs in human patients. When the results of treatment are reported completely and accurately the data may be helpful to patients and physicians as well as to FDA. Such information can lead to warnings against dangerous unapproved uses, or, on the other hand, to acceptance of previously unknown uses.

Physicians have been concerned that the failure to follow the labeling of a drug may render them unduly liable for malpractice. Although labeling, along with medical articles, texts, and expert opinion, may constitute evidence of the proper practice of medicine, it alone is not controlling on this issue.

The labeling is not intended either to preclude the physician from using his best judgment in the interest of the patient, or to impose liability if he does not follow the package insert. A physician should recognize, however, that the package insert represents a summary of the important information of the conditions under which the drug has been shown to be safe and effective by adequate scientific data submitted to FDA.

When the unapproved use of an approved new drug becomes widespread or endangers the public health, FDA is obligated to investigate thoroughly and to take whatever action is warranted to protect the public. Several alternative courses of action are available to FDA under these circumstances, depending upon the specific facts of each case.

These alternatives include: Requiring a change in the labeling to warn against or to approve the unapproved use, seeking substantial evidence to substantiate the use, restricting the channel of distribution, and even withdrawing approval of the drug and removing it from the market in extreme cases. When necessary, FDA will take whatever action may be required to bring possible harmful use of an approved drug under control.

FDA regulations require the labeling to contain information with respect to all intended uses of the drugs. Thus, when a manufacturer or his representative, or any person in the chain of distribution, does anything that directly or indirectly suggests to the physician or patient that an approved drug may properly be used for unapproved uses for which it is neither labeled nor advertised, that action constitutes a direct violation of the Act and is punishable accordingly.

FDA believes it important that the public, the medical profession, and the pharmaceutical industry fully appreciate the statutory provisions enacted by Congress that are controlling under these circumstances. Therefore it has proposed a regulation which sets forth the principles enunciated in this article. The full text of the regulation is available by writing to the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, Maryland 20852.

FDA welcomes the views of physicians on this proposed regulation. Comments may be sent to the above address.

FDA Drug Bulletin, October 1972

Proposed CMA Constitutional Amendments

FOR ACTION IN 1973

Six Constitutional amendments were introduced in the 1972 House of Delegates. Under the terms of the Constitution, these amendments must lie on the table until the next regular meeting of the House of Delegates.

These proposed amendments are shown here for the information of the membership. In addition, the proposed Constitutional amendments are required to be printed in two issues of CALIFORNIA MEDICINE before they come before the House of Delegates for action.

* * *

ARTICLE II, SECTION 1—CLASSES OF MEMBERS

Constitutional Amendment 1-72 Committee G

Introduced by: Paul Scholten, M.D.

WHEREAS, "free choice" is a prime tenet of the medical profession; and

WHEREAS, "required membership" is directly contrary to this prime tenet; and

WHEREAS, the recent poll conducted by the CMA as well as referendums by component medical societies indicated the desire of a substantial group of physicians to exercise their "free choice"; now, therefore, be it

Resolved: That the Constitution of the CMA be amended to include the classification of Independent Member. Such member would pay full dues to his component medical society and receive full benefits therefrom; such member *may* join the CMA by paying full dues, from which he would receive full benefits; and, be it further

Resolved: That Article II, Section 1, be amended by adding the word in italics: "The members of this Association shall consist of Active, Associate, *Independent*, Honorary, Retired, Life and Affiliate members."

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

ARTICLE I, SECTION 3—VOLUNTARY MEMBERSHIP IN CMA AND AMA BY A MEMBER OF A COMPONENT COUNTY MEDICAL ASSOCIATION

Constitutional Amendment 2-72 Committee G

Introduced by: James W. Goettle, M.D.
Representing: Tulare County Medical Society

WHEREAS, the present bylaws of the CMA make membership in the AMA and CMA compulsory to all members of a component county medical society; and

WHEREAS, the medical profession has always vigorously defended the concept of "freedom of choice" in health care, but will not give this freedom of choice to its members as numerous other states now do; and

WHEREAS, freedom of choice has always been beneficial to professional people in the long run, for it makes the leaders of such organizations more responsive to members' desires as the history of our country has so demonstrated to the world; now, therefore, be it

Resolved: That the CMA Constitution be amended to read as follows: (Article I, Section 3) members of local county medical societies in the State of California have the freedom to decide individually whether they wish to join the CMA or AMA, singly or in combination.

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

* * *

ARTICLE I, SECTION 3—PROPOSED CALIFORNIA MEDICAL ASSOCIATION CONSTITUTIONAL AMENDMENT PERMITTING VOLUNTARY MEMBERSHIP IN CMA AND AMA BY A MEMBER OF A COMPONENT COUNTY MEDICAL ASSOCIATION

Constitutional Amendment 3-72 Committee G

Introduced by: Allan K. Briney, M.D.
Representing: Los Angeles County

WHEREAS, the present Bylaws of the California Medical Association make membership in the

California Medical Association and the American Medical Association compulsory to all members of a component county medical society; and

Whereas, we, as a profession, vigorously defend the principle of "freedom of choice" in health care, yet deny individual members of county medical societies the freedom of deciding whether or not they wish to belong to the California Medical Association or American Medical Association; and

Whereas, each physician is quite capable of deciding whether there are sufficient advantages or insufficient advantages to maintaining membership in all three organizations; and

Whereas, mandatory membership in one organization (CMA and AMA) in order to maintain membership in another (local medical society) significantly interferes with the privilege of setting priorities as to organizational commitments, such as belonging to specialty societies; and

Whereas, in forty states a local county medical association member may decide for himself whether he also wishes to maintain membership in the state and national medical associations; e.g., New York and Massachusetts; and

Whereas, professional liability insurance carriers have no requirements about California Medical Association or American Medical Association membership for coverage of a county medical society member; and

Whereas, in a free and democratic society it would seem reasonable and consistent that membership in all medical societies should be voluntary, with each society attracting members on its own merits; and

Whereas, when a local county medical association collects dues for a state and national medical association, the individual dues-payer tends to lump all these dues together as "county medical society dues", feeling he may not be "getting his money's worth"; and

Whereas, there is widespread feeling among local county medical association members that the CMA and AMA have long ago lost their "grass roots" contact and cannot speak authoritatively for the medical profession; and

Whereas, recent polls of the Los Angeles, Orange, San Diego and San Francisco County Medical Associations have overwhelmingly favored voluntary membership by an average of four to one, as opposed to compulsory membership; and

Whereas, a national poll by *Medical Opinion* magazine, published in November, 1971, showed 82% favoring voluntary membership in the American Medical Association; and

Whereas, results of the recent CMA opinion poll are inconclusive and misleading, due to substitution of the words *involuntary* and *compulsory* specified in Bylaws Amendment 22-71 authorizing the poll, by the words *separate* and *unified;* now, therefore, be it

Resolved: That Article I, Section 3, be amended as follows:

> This Association is an organization composed of the component societies and their members who are members of this Association, the House of Delegates, the Council, the Scientific Board, the Scientific Assembly, Bureaus, Commissions and Standing Committees.

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

* * *

ARTICLE III, PART A, SECTION 1(d)—VOTING PRIVILEGES FOR SCIENTIFIC BOARD REPRESENTATIVES IN THE HOUSE OF DELEGATES

Constitutional Amendment 4-72 Committee G

Introduced by: Council

Resolved: That Article III, Part A, Section 1 (d)—House of Delegates composition shall be amended by deleting the words in brackets and adding the words in italics, so that this Subsection shall now read:

"(d) Ex officio, [without] *with* the right to vote, [eighteen (18)] *twenty-one (21)* members of the Scientific Board selected as provided in the Bylaws; and . . ."

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

* * *

DELEGATES AND ALTERNATES TO AMA SHALL BE EX OFFICIO DELEGATES OF CMA

Constitutional Amendment 5-72 Committee G

Introduced by: Lawrence E. Reck, M.D.
Representing: 1st District

Resolved: That Article III, Part A, Section 1, be amended by adding a new sub-section (f) which reads as follows:

(f) *Ex officio, without the right to vote, the officers, the delegates and alternate delegates to the American Medical Association, who are not otherwise members of the House of Delegates of this Association.*

ACTION: Adopted above substitute Constitutional Amendment No. 5-72 as substitute for Resolution No. 62-72. Tabled for one year. To be acted upon at the 1973 House of Delegates.

ARTICLE III—GOVERNMENT OF THE ASSOCIATION
PART A—HOUSE OF DELEGATES—COMPOSITION
SECTIONS 1, 2, 4

Constitutional Amendment 6-72 **Committee G**

Introduced by: E. Kash Rose, M.D.

Resolved: That Article III, Part A, Section 1, be amended by adding a new sub-section (g) which reads as follows: *(g) Delegates elected by duly enrolled medical students in good standing at accredited schools of medicine in California;* and, be it further

Resolved: That Article III, Part A, Section 2, be amended by adding the words in italics, to read as follows:

As the Bylaws shall further provide, the duly enrolled medical students in good standing at each accredited school of medicine located in California shall be entitled to elect one delegate from each such school; and, be it further

Resolved: That Article III, Part A, Section 4, be amended by adding the words in italics, to read as follows:

Delegates and alternates elected from each school of medicine shall serve for a term of one year.

ACTION: Tabled for one year. To be acted upon at the 1973 meeting of the House of Delegates.

SCIENTIFIC EXHIBITS

102nd Annual Session of the

California Medical Association

and Second Western States Invitational Scientific Assembly

March 10-14, 1973 **Disneyland Hotel, Anaheim**

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102nd

Annual Session

California Medical Association

and Second Western States Invitational Scientific Assembly

March 10-14, 1973 • Disneyland Hotel • Anaheim

Full program information will appear in the January issue. A list of some of the distinguished out-of-state speakers participating in Section Meetings and Special Conferences follows:

- *Allergy*

  John E. Salvaggio, M.D., Department of Internal Medicine, Tulane University School of Medicine, New Orleans

- *Anesthesiology, Otolaryngology*

  John Tucker, M.D., Professor of Otolaryngology and Bronchoesophagology, Hahneman Medical College, Philadelphia

- *Chest Diseases, Internal Medicine*

  Juro Wada, M.D., Professor of Surgery, University of Medicine, Sapporo, Japan; Visiting Professor, Thoracic Surgery, Vanderbilt University School of Medicine, Nashville, Tennessee

  Albert Starr, M.D., University of Oregon Medical School, Portland

- *Chest Diseases, Industrial Medicine*

  LeRoy Lapp, M.D., Chief, Medical Research Branch, Appalachian Laboratory for Occupational Respiratory Diseases, Department of HEW, US Public Health Service, Morgantown, West Virginia

  I. J. Selikoff, M.D., Mount Sinai School of Medicine of The City University of New York, New York City

  George H. R. Taylor, AFL-CIO Standing Committee on Safety and Occupational Health, Washington, D.C.

- *General Practice*

  Robert Brittain, M.D., Inter-Hospital Education Association, Englewood, Colorado

  Harold Cross, M.D., Promis Clinic, Hampden Highlands, Maine

- *General Practice, Plastic Surgery*

  Paul Daines, M.D., Coordinator, NRMP Intermountain District for Continuing Medical Education, Montpelier, Idaho

- *General Surgery*

  Edward R. Woodward, M.D., Professor and Chairman, Department of Surgery, University of Florida College of Medicine, J. Hillis Miller Health Center, Gainesville

- *Obstetrics and Gynecology*

  Paul C. MacDonald, M.D., Professor and Chairman, Department of Obstetrics and Gynecology, University of Texas Southwestern Medical School at Dallas

- *Ophthalmology*

  Eugene R. Folk, M.D., Associate Professor of Ophthalmology, Abraham Lincoln School of Medicine, University of Illinois, Chicago; Attending Ophthalmologist on the Motility Service, Illinois Eye and Ear Infirmary, Skokie

- *Orthopedics, Pediatrics, Radiology*

  Walter P. Blount, M.D., Emeritus Clinical Professor of Orthopedics, Medical College of Wisconsin, Milwaukee

  Fred Silverman, M.D., Professor of Radiology, University of Cincinnati College of Medicine

- *Pediatrics*

  Alan K. Done, M.D., Bureau of Drugs, Food and Drug Administration, Washington, D.C.

- *Physical Medicine and Rehabilitation*

  Jerome Gersten, M.D., Professor and Chairman, Department of Physical Medicine and Rehabilitation, University of Colorado Medical Center, Denver

- *Cancer Symposium*

  Alfred S. Ketcham, M.D., Clinical Director and Chief of Surgery Branch, National Cancer Institute, Bethesda, Maryland

  Alando J. Ballantyne, M.D., Associate Professor of Surgery, University of Texas Medical School at Houston; Surgeon, Head and Neck, Department of Surgery, M. D. Anderson Hospital and Tumor Institute, Houston

  Harry S. Goldsmith, M.D., Samuel D. Gross Professor of Surgery; Chairman, Department of Surgery, Jefferson Medical College, Philadelphia.

- *Alcoholism/Dangerous Drugs Conference*

  Karl J. Deissler, M.D., Luzern, Switzerland

  Roger O. Egeberg, M.D., Special Assistant to the President on Health Affairs; Secretary of HEW on Health Matters, Department of Health, Education and Welfare, Office of the Secretary, Washington, D.C.

  R. Edward Quass, M.D., Tucson, Arizona

application for HOTEL ACCOMMODATIONS
ONE-HUNDRED-SECOND *Annual Session*

CALIFORNIA MEDICAL ASSOCIATION
And
Second Invitational Western States Scientific Assembly

MARCH 10-14, 1973

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FRIDAY AFTERNOON, MARCH 9

SCIENTIFIC SESSIONS.. BEGIN SATURDAY MORNING, MARCH 10
HOUSE OF DELEGATES OPENING SESSION............................SATURDAY AFTERNOON, MARCH 10

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1. Fill in the form below *completely* for room accommodations at the CMA's 1973 Annual Session. There are only a limited number of rooms available. Your choice of accommodations will be better if your request is for rooms to be occupied by two or more persons.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations, except for suites, must be made through the Disneyland Hotel, 1441 S. West Street, Anaheim, California 92802, by February 9, 1973.
4. ALL SUITE RESERVATIONS MUST BE CLEARED THROUGH THE CMA CONVENTION OFFICE, SAN FRANCISCO. *IF YOU ARE REQUESTING A SUITE, DIRECT YOUR REQUESTS TO: CMA CONVENTION OFFICE, 693 SUTTER STREET, SAN FRANCISCO, CA. 94102.*
5. CANCELLATIONS: Please notify Disneyland Hotel, 1441 S. West Street, Anaheim, of all cancellations. CHANGES: All other changes to be made directly with hotel at all times.
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Single Bedroom $..............Twin-Bedded $................Double Bed $............Suite $..........

Arrival (date) .... Hour ....a.m p.m. Departure (date) .... Hour ....a.m. p.m.

THE NAME AND ADDRESS OF EACH HOTEL GUEST MUST BE LISTED. Include names and addresses of *each* person in a double or twin-bedded room, and names and addresses of *all other persons* for whom you are requesting reservations.

Your Name: ....Officer?..... Delegate? ..... Alternate?..... Speaker? .....

Address: .... County ....

City and State .... Zip Code ....

GUESTS' NAMES AND ADDRESSES:

....

....

....

In Memoriam

Persons wishing to do so may make contributions to the Physicians' Benevolence Fund to honor the memory of a member who has died. Members of the family will be notified that such a contribution has been made and the name of the donor will be supplied.

Checks should be addressed to Physicians' Benevolence Fund, Inc., California Medical Association, 693 Sutter Street, San Francisco, Ca. 94102.

DEMPSEY, EDMUND VINCENT, San Francisco. Died October 10, 1972 in Redwood City, aged 57. Graduate of University of Michigan Medical School, Ann Arbor, 1943. Licensed in California in 1946. Doctor Dempsey was a member of the San Francisco Medical Society.

⁂

DWORSKY, RICHARD, Whittier. Died September 9, 1972 in San Francisco of renal failure, aged 50. Graduate of The University of Nebraska College of Medicine, Omaha, 1957. Licensed in California in 1958. Doctor Dworsky was a member of the Los Angeles County Medical Association.

⁂

GREENMAN, ROBERT ALVIN, Chester. Died September 15, 1972 in Reno, aged 73. Graduate of State University of Iowa College of Medicine, Iowa City, 1929. Licensed in California in 1931. Doctor Greenman was a member of the Lassen-Plumas-Modoc-Sierra County Medical Society.

⁂

HEGLIN, JOHN DAVID, Torrance. Died October 8, 1972 in Torrance, aged 52. Graduate of University of Southern California School of Medicine, Los Angeles, 1957. Licensed in California in 1958. Doctor Heglin was a member of the Los Angeles County Medical Association.

⁂

INCE, WILLIAM T., Twentynine Palms. Died October 6, 1972 in Twentynine Palms, aged 63. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1935. Licensed in California in 1935. M.D. degree from California College of Medicine, 1962. Doctor Ince was a member of the San Bernardino County Medical Society.

⁂

LIGHTBODY, KENNETH A., Long Beach. Died October 13, 1972 in Long Beach, aged 55. Graduate of the University of Nebraska College of Medicine, Omaha, 1941. Licensed in California in 1945. Doctor Lightbody was a member of the Los Angeles County Medical Association.

NEFF, FLOYD EUGENE, Compton. Died September 11, 1972 in Paramount, aged 70. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1929. Licensed in California in 1929. Doctor Neff was a member of the Los Angeles County Medical Association.

⁂

NERI, MARIO PHILIP, San Jose. Died October 19, 1972 in San Francisco of injuries received in automobile accident, aged 45. Graduate of Harvard Medical School, Boston, 1957. Licensed in California in 1964. Doctor Neri was a member of the Santa Clara County Medical Society.

⁂

NICHOLS, HARRY C., Bellflower. Died August 29, 1972, aged 84. Graduate of the Creighton University School of Medicine, Omaha, 1911. Licensed in California in 1926. Doctor Nichols was a member of the Los Angeles County Medical Association.

⁂

NORMAN, CLYDE W., San Diego. Died October 15, 1972 in San Diego, aged 58. Graduate of the Ohio State University College of Medicine, Columbus, 1941. Licensed in California in 1946. Doctor Norman was an associate member of the San Diego County Medical Society.

⁂

NOWACK, JACQUES, Arcadia. Died September 22, 1972 in Arcadia, aged 57. Graduate of University of California Medical School, Berkeley-San Francisco, 1943. Licensed in California in 1943. Doctor Nowack was an associate member of the Los Angeles County Association.

⁂

O'CONNOR, GERALD BROWN, San Francisco. Died October 30, 1972 in San Francisco, aged 72. Graduate of St. Louis University School of Medicine, 1925. Licensed in California in 1925. Doctor O'Connor was a member of the San Francisco Medical Society.

⁂

SEID, MARTIN J., San Francisco. Died October 5, 1972 in San Francisco, aged 83. Graduate of Cooper Medical College, San Francisco, 1911. Licensed in California in 1911. Doctor Seid was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

⁂

WARD, ALSIE GRAY, Downey. Died May 26, 1972 of coronary artery thrombosis, aged 75. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1942. Licensed in California in 1942. Doctor Ward was a member of the Los Angeles County Medical Association.

BOOK REVIEWS

California Medicine does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CHEST INJURIES—Physiologic Principles and Emergency Management—Emil A. Naclerio, M.D., F.A.C.S., F.C.C.P., F.A.C.C., Attending Thoracic Surgeon, Department of Surgery, Harlem Hospital Center, College of Physicians and Surgeons of Columbia University; Attending Thoracic Surgeon, Columbus Hospital, New York, New York. Grune & Stratton, Inc., 757 Third Avenue, New York City (10017), 1971. 383 pages, $28.50.

Chest Injuries—Physiological Principles in Emergency Management is a compilation of the author's own experiences in emergency medicine, methods of treatment and approaches toward patient care with traumatic thoracic problems. The book is somewhat tedious because of its loose organization, casual relationship of one subject to another, and tendency toward repetition. There are many clinical "pearls" the author includes in his book which enhance its usefulness. However, the absence of an annotated bibliography, inclusion of confusing metaphors and lack of indepth refinement in up-to-date treatment of certain major problems reduce the value of the book. Many of the techniques the author describes are presented in a lucid and interesting form. However, there is inappropriate introduction of x-rays and supporting diagrams without sufficient description to make them complimentary to the accompanying text. There is no question that the author's experience pervades the entire book. Upon this alone, the book is worthy of perusal. Based upon the other factors noted above and its cost, I doubt that it will become universally accepted as a basic text in the care of traumatic chest injuries.

Edward J. Hurley, m.d.

* * *

HANDBOOK OF POISONING—Diagnosis and Treatment—Seventh Edition—Robert H. Dreisbach, M.D., Ph.D., Professor (Emeritus) of Pharmacology, Stanford University School of Medicine, Stanford, California. Lange Medical Publications, Drawer L, Los Altos, Ca. (94022), 1971. 515 pages, $6.00.

This is the 7th Edition of this popular book on poisoning by Dr. Dreisbach, Professor (Emeritus) of Stanford University. It is expanded and the tabulation of material is of considerable help to the physician who must make up his mind concerning the great variety of agents which can cause acute poisoning in children. There has been an attempt to include general statements on environmental intoxication and this in itself does not improve the contents of the book. There are especially good sections on treatment of intoxications from poisonous plants and animals. Unfortunately, there are included a number of agents which are only of passing curiosity and are never encountered in clinical toxicology. The text does suffer somewhat also from the obvious lack of clinical experience of the author. Most texts on the treatment of poisoning are written by pharmacologists and basic scientists who are not in practice. Nevertheless, this book has much to recommend it and its convenient size makes it a handy addition to physicians' emergency equipment. There are short and well chosen bibliographic references.

Recommended for general practitioners and pediatricians.

Charles H. Hine, m.d.

KIDNEY AND URINARY TRACT INFECTIONS—Edited by Mitchell Kory, Ph.D., and S. O. Waife, M.D., Eli Lilly and Company, Indianapolis, In. (46206), 1971. 136 pages, available at no charge to interested medical students, house officers, and practicing clinicians.

The Lilly Research Laboratories with the aid of a number of prominent well-qualified nephrologists have published an attractive primer relating to the kidney and urinary tract infections. Much practical information is provided concerning etiology, techniques of laboratory diagnosis (including paracentesis of the urinary bladder and x-ray of the urinary tract), principles of antimicrobial therapy, structure and function of the kidney and management of renal failure, all of which is of potential value to all interested in urinary tract infections; that is to say, most medical students and physicians since urinary tract infections next to respiratory are among the most frequent.

Criticism that can be made of this primer is that like all primers, in the interest of brevity, not all sides of questions can be thoroughly enough covered. However, references are provided for further reading. This book is highly recommended by this reader.

James Hopper, Jr., m.d.

* * *

BASIC BIOCHEMISTRY—Third Edition—Max E. Rafelson, Jr., Ph.D., Associate Dean, Biological and Behavioral Sciences and Services, and Professor of Biochemistry, Rush Medical College, Rush-Presbyterian-St. Luke's Medical Center, Chicago; Stephen B. Binkley, Ph.D., Dean, Graduate College, and Professor Biological Chemistry, University of Illinois Medical Center, Chicago; and James A. Hayashi, Ph.D., Professor Biochemistry, Rush Medical College. The Macmillan Company, 866 Third Avenue, New York, N.Y. (10022), 1971. 406 pages, $7.95, paperback, and $11.00, hardbound.

In a good book for a comprehensive initial biochemistry course, Rafelson, Binkley and Hayashi have stressed the structure of biomolecules and the details of a wide range of metabolic pathways. Details are given, for example, of the structure of four different porphyrin molecules and of the biosynthesis of all of the amino acids. The reader is presented the difference between lysine biosynthesis in fungi and bacteria. The book would be most suitable for students with a strong interest in chemistry. For students in biological fields a course presented with this book as a guideline would be more stimulating if given simultaneously with a cell biology course. Teachers of basic biochemistry courses should give this book serious consideration. As a paperback at $7.95 this is a good buy.

Donal A. Walsh, ph.d.

* * *

SYMPOSIUM ON THE HAND—Volume Three—Editors: Lester M. Cramer, D.M.D., M.D., Professor and Chairman, Section of Plastic Surgery, Temple University Health Sciences Center, Philadelphia; Robert A. Chase, M.D., Professor and Executive, Department of Surgery, Stanford University Medical Center, Palo Alto. The C. V. Mosby Company, Publishers, 11830 Westline Industrial Drive, St. Louis, Mo. (63141), 1971. 287 pages, $35.75.

This volume represents part of an ongoing series in the field of hand surgery and is a compilation of the material presented at a 3-day symposium held at Stanford University in 1970.

There are 23 papers covering a wide variety of currently controversial subjects presented by 26 leading hand surgeons. Each article is followed by a discussion section which proves to be extremely interesting in that questions on practical clinical management are posed and answered.

Included are such topics as hand replantation, early versus delayed tendon repair, principles of treatment of finger tip injuries, and burns.

In all, this book is a very readable, very valuable adjunct to the library of anyone involved in surgery of the hand.

Franklin L. Ashley, m.d.

* * *

PATHOLOGY—Sixth Edition—Volumes I and II—Edited by W. A. D. Anderson, M.A., M.D., Professor of Pathology and Chairman of the Department of Pathology, University of Miami School of Medicine, Miami, Fla., Director of the Pathology Laboratories, Jackson Memorial Hospital, Miami, Fla. The C. V. Mosby Company, 11830 Westline Drive, St. Louis, Mo. (63141), 1971. 1862 pages, $29.50.

I always enjoy revisiting the haunts of my youth usually to find things not quite the same, but interesting just the same; likewise, with textbooks such as Harrison's *Textbook of Medicine* or Anderson's *Pathology*.

This is the fourth edition of Anderson which I have used since my student days, and certainly the best. The list of contributing authors has been revised and increased from 39 to 45, and now includes many more recognized authorities in the specialties of pathology.

There are major revisions in the chapters on inflammation, response to injury, eye, hematopoietic system, respiratory tract, urinary tract, endocrine glands, and the neuromuscular systems. The new material includes concepts arising from progress in ultrastructure, immunopathology, and biochemistry. The references are extensive.

I found the sections on infectious diseases, kidney, eye, skin, and bone particularly well done. And, I am pleased to find the chapters on the hematopoietic system and thymus entirely new, reflecting current concepts of disease in these organs, especially in relation to neoplastic processes.

The orientation of this book is to explain classical pathologic anatomy (morphology) in the light of altered physiology. This, I think, makes for a lucid, timely text. For me, this sixth edition of Anderson's *Pathology* remains the standard American textbook of pathology.

Samuel J. Corman, m.d.

* * *

RADIOLOGY OF THE SKULL AND BRAIN—Volume I—The Skull—Edited by Thomas H. Newton, M.D., Professor of Radiology, Neurology and Neurosurgery, Chief, Section of Neuroradiology, University of California, San Francisco, School of Medicine; and D. Gordon Potts, M.D., Professor of Radiology, Cornell Medical College, Attending Radiologist, The New York Hospital, New York City. The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis, Mo. (63103), 1971. 874 pages, $78.50.

This two-book set on the skull represents the first volume of a proposed three volume work on *Radiology of the Skull and Brain.* The next volume will deal with angiography, and the third volume with air studies, neuropathology, and isotope studies. The spinal cord will not be included. The raw bulk of these volumes offers some evidence of advances in the specialty.

Many of these advances are due to refinements in roentgen technique. These refinements of technique have greatly expanded our knowledge of neuroanatomy. It is even claimed that cerebral angiographers now have a "vein of the month" club. These advances include the use of small focal spots, higher powered generators, selective angiography, magnification techniques, multidirectional tomography, and subtraction techniques. A number of chapters deal with these techniques. Pott's chapter on Radiographic Techniques and Projections is of some interest but does not attempt to cover the routine or special views of the skull.

Thirty-seven authors have contributed to the volume. It is divided into a number of parts, each with several separate chapters. Each chapter has its own list of references. Following a History of Neuroradiology by Erik Lindgren, who himself must be part of that history, we find parts on Technical Aspects of Skull Roentgenology, Skull Maturation, Skull Vault, Skull Base, Orbit, Congenital Anomalies of the Skull, and Other Diseases Involving the Skull. Reproductions are of good quality. However, some of the illustrations will challenge the reader's wit and even his sanity. We find as markers: solid black arrows, open black arrows, solid white arrows, open white arrows, double black arrows. These are all crowded onto 2 by 3 inch reproductions of radiographs with a separate identifying legend below. The consequent referring back and forth from illustrations to legend is confusing.

John Campbell has enlivened his rather detailed chapter on Craniofacial Anomalies with some photographs of pre-Columbian pottery. He ascribes a number of anomalies to these ancient Indian figures, but the reviewer believes that the appearances represent nothing more than the customary stylization and artistic license of the Tarascan potters. The author also includes a cartoon of Andy Gump, and he now stands labelled as a sad case of Pierre Robin syndrome. In addition, there is a depressingly lively photographic gallery of the varied genetic aberrations described.

Some new insights on Skull Trauma are provided by Bergeron and Rumbaugh. Traumatic cortical aneurysms, fractures through the floor of the sella turcica, and fine tomographic depictions of disruptions of the middle ear ossicles due to skull fracture are shown.

All in all this is a useful reference work which deserves a place in the libraries of those involved in the field.

Robert B. Engle, m.d.

* * *

HERMAPHRODITISM, GENITAL ANOMALIES AND RELATED ENDOCRINE DISORDERS—Second Edition—Howard W. Jones, Jr., M.D., Professor of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Gynecologist, Johns Hopkins Hospital; William Wallace Scott, M.D., Ph.D., Professor of Urology, Johns Hopkins University School of Medicine, Urologist-in-Charge, Johns Hopkins Hospital. The Williams & Wilkins Company, 428 E. Preston Street, Baltimore, Md. (21202), 1971. 564 pages, $33.50.

This is the latest edition of a work begun by Dr. Hugh Young in 1937, completely redone by Jones and Scott in 1958 and now rewritten by them with the help of other experts, many of whom contributed to the 1958 volume.

Embryonic sexual differentiation is reviewed in an excellent chapter, but that dealing with classification is deficient in relegating etiology and criteria to a single table. One misses the clinically useful approach of Federman (ref. 1), but the subsequent chapters detailing each syndrome add depth by their content of case histories with diagnostic details.

The chapters on cryptorchidism and hypospadias are disappointing, but these disorders are at the margin of intersexuality. Many of the operations depicted in the chapter on hypospadias are out-of-date, and much reliance is placed on one-stage procedures. The authors fail to mention that when malignancy occurs after orchiopexy, it is in children operated upon near the time of puberty. They do not separate bilateral and unilateral cases when discussing hormonal therapy. However, they do conclude that early operation is desirable.

In sum, this is an excellent volume, especially useful for the pediatrician and urologist, since it is based on the great clinical experience obtained in the Johns Hopkins Hospital.

Frank Hinman, Jr., m.d.

1.—Federman DD: Abnormal Sexual Development—A Genetic and Endocrine Approach to Differential Diagnosis. Philadelphia, W.B. Saunders Company, 1967

Consultants for *California Medicine* in 1972

The editors wish to acknowledge with appreciation the valued services, beyond those of members of the Editorial Board, given by the following persons to the Journal during the past year.

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